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Original Communications

ON THE PROPHYLAXIS OF HEMOLYTIC DISEASE OF THE NEWBORN

DONALD H. KARIHER, M.D., ROCHESTER, N. Y., WITH THE
TECHNICAL ASSISTANCE OF DOROTHY I. MILLER

*(From the Department of Obstetrics and Gynecology the University of Rochester
School of Medicine and Dentistry)*

IT WOULD seem that it is now possible to diagnose hemolytic disease of the newborn in the as yet unborn infant in nearly all cases.¹ This can be done by routinely testing the sera of all Rh-negative mothers during their pregnancies for the presence of one or more of the Rh antibodies, and obtaining titers of the amount of antibody if any is present.² Being aware before delivery of the fact that an infant with hemolytic disease of the newborn is to be delivered, one can make preparations for the proper treatment of the infant following its birth. This preparation and treatment resolves itself into having available Rh-negative blood of the proper group, and transfusing the infant immediately at birth or as soon thereafter as seems justified by the condition of the baby, and particularly by the red blood cell and hemoglobin levels. Repeated blood transfusions are nearly always necessary.

By this means the mortality rate in liveborn infants suffering from hemolytic disease of the newborn has been reduced to between 9 per cent³ and 33 per cent.⁴ Obviously, this form of treatment of the infant, helpful as it has been, is far from being satisfactory. Aside from failing in still a large percentage of liveborn infants, it of course is useless if the infant is stillborn or if the patient aborts the pregnancy early during its course. The ideal treatment, which would actually be prophylactic in nature, is the treatment of the mother during her pregnancy. This treatment could be directed at one of three objectives: (1) the prevention, by some chemical means, of the antigen-antibody reaction from going to completion. This, of course, is the essential reaction in the production of hemolytic disease of the newborn; (2) the absorption of the antibody as soon as it is formed by means of Rh haptene injections; or (3) inhibition of antibody by some immunologic means.

NOTE: The Editors accept no responsibility for views and statements of authors as published in their "Original Communications."

Wiener has suggested this⁵ objective in his theory of "competition of antigens." He believes that if two or more antigens of unequal potency are given an individual, that individual will produce an antibody against the stronger antigen, and produce little, if any, against the weaker antigen. He believes that since the Rh antigen is a relatively weak one, pertussis and typhoid vaccines given at intervals during the course of a patient's pregnancy might inhibit or prevent the formation by that patient of the Rh antibodies.

Following this line of reasoning we gave one patient weekly injections of A and B specific substances (Eli Lilly and Co.), which are relatively strong antigens during the last six months of pregnancy without having any effect on the course of her Rh-antibody production, and with the result that she delivered an infant which died from hemolytic disease of the newborn on its fourth day of life.

To the writer's knowledge, the Rh haptene has not been obtained in any form which would make it useful clinically. Thus, the second of the above objectives is probably not attainable at present.

The purpose of this communication is to present three cases which have been treated with the first objective in mind, that is, the prevention by some chemical means of the antigen-antibody reaction going on to completion. In all three cases the patients have previously delivered one or more infants which have died of hemolytic disease of the newborn. In two of these cases the patients have, following treatment, delivered infants which appeared normal at birth and remained so during the period of observation. In the third case the infant had hemolytic disease of the newborn, but survived following repeated transfusions. The treatment consisted of weekly intramuscular injections of 2.0 c.c. of ethylene disulfonate (Allergosil Brand)* during the last three, four, and six months of the pregnancies, respectively. In two of the cases the hemolytic disease in the previous pregnancies was due to an Rh incompatibility, while in the other case it was due to an O-A incompatibility, the mother being group O and the infant group A. Because of the small number of cases, this report is being published with the hope that others will attempt to corroborate the findings presented here. The relative paucity of suitable material would make the collection of a large series of cases by any single clinic a very prolonged experiment. This report is not being published as a cure for hemolytic disease of the newborn.

Theory

Knowing that the production of hemolytic disease of the newborn in affected infants is essentially an antigen-antibody reaction, the idea suggests itself that if one portion of the reaction is eliminated, the reaction then cannot go to completion. Obviously, the antigen on the fetal red cells cannot be eliminated. Some process then of preventing the production of antibody, or of destroying it as fast as it is produced must be achieved. We have observed⁶ that out of several thousand tests of the sera of pregnant Rh-negative women for the agglutinating and conglutinating antibodies, in only two instances have

*This material was very generously supplied for experimental work by the Spicer-Gerhart Company, Pasadena, California.

we found one or more of the Rh antibodies of any degree in the mother without having that mother later deliver an infant with hemolytic disease of the newborn. Likewise, since the institution of routinely testing the sera of all pregnant women for the presence or absence of both agglutinating and conglutinating antibodies, no instances have been found where a diseased infant was born from a mother who had not previously demonstrated the presence of one or more of the Rh antibodies in her serum, except in those instances where the disease was due to some blood incompatibility other than Rh.⁴ We have also observed, as have others, that the level of Rh antibody titer in the mother bears no correlation with the severity of the disease in the infant. It would seem reasonable, however, in view of the above statements, that if the Rh antibody could be eliminated from the maternal circulation, the infant should be normal at birth and remain so.

To this end, a drug which has been used in allergic states was employed, mainly ethylene disulfonate (Allergosil Brand). Its use in allergic conditions was based on the conclusion of the British and Belgian observers; Evans, Bodman, and Maisin,⁷ that in allergic states there is some abnormality of the cellular metabolism of carbohydrate, which in turn is due to the absence of a certain oxidation catalyst in the body. These workers also concluded that ethylene disulfonate would act as an oxidation catalyst and thus restore the cellular carbohydrate metabolism to normal, which in turn would alleviate the allergic manifestations. They present both case histories and animal experiments in support of their conclusions. They feel that a physiologic dilution of the drug is between $1:10^{-10}$ and $1:10^{-18}$, and used a dilution of $1:10^{-15}$ in their case studies and animal experiments. Fisk, Small, and Foord,⁸ using ethylene disulfonate in an attempt to protect guinea pigs against anaphylactic shock, found that it did not produce a significant degree of protection. In fact, they found that distilled water alone produced approximately the same amount of protection.

In the present study, the dilution of the chemical was $1:10^{-15}$ in triple distilled water, as packaged by Spicer-Gerhart under the name ethylene disulfonate (Allergosil Brand). This great dilution means that each 2.0 c.c. injection (the dosage used) contains 0.000000000002 mg. of ethylene disulfonate. It would seem that this dilution is practically distilled water, and it may be that the results to be reported are due to the intramuscular injection of distilled water rather than to the infinitesimal amount of ethylene disulfonate in the solution. However, it is not within the scope of this paper to discuss the theoretical chemical reactions involved, but merely to report the results. Recently⁹ the Council on Pharmacy and Chemistry of the American Medical Association has published a lengthy discussion of ethylene disulfonate (Allergosil Brand), and has found it not acceptable for inclusion in *New and Nonofficial Remedies*.

Experimental

In Rochester, New York, a plan has been in operation since Oct. 1, 1945, for carrying out routine Rh determinations on all pregnant women.¹ The sera of all Rh-negative patients are studied at intervals throughout the course of their pregnancies for the detection of one or more of the Rh antibodies. It was from this source that the three cases to be described in detail were chosen. They were chosen in each instance because of a history of hemolytic disease of the newborn in a previous pregnancy, proved by clinical and pathologic studies. These patients were in varying stages of their pregnancies when this study was started, and in each instance it was felt that another infant would be born with hemolytic disease. This was thought to be so, since in each instance the patient already carried a high titer of Rh (2 cases) or A (1 case) antibody in her serum. In each case 2.0 c.c. of ethylene disulfonate (Allergosil Brand)

in a dilution of 1:10⁻¹⁵ in triple distilled water was given intramuscularly at weekly intervals until labor was established. This meant that the first patient (case 1) received 12 injections, the second patient (case 2) received 10 injections and the third patient (case 3) 20 injections. Weekly samples of blood were withdrawn from the patient, and the serum so obtained was titered for the level of the particular antibody in question. Prior to titration, the sera were inactivated by placing them in an incubator at 56° C. for thirty to forty-five minutes. The titrations were carried out in 6 mm. tubes by the dilution method as described by Wiener,¹⁰ using pipettes, and making very careful dilutions. When the agglutinating antibody titration was being carried out, saline was the suspending medium and diluent for the Rh-positive red blood cells. When the "conglutinating" antibody¹¹ titer was being studied, serum from a group AB individual was used as the suspending medium and diluent. Although new batches of saline were used frequently during the course of the study, the AB serum was a constant. The red blood cells used as test cells in the anti-Rh titrations were group O Rh positive and were always used fresh from the same individual. It was not found possible to obtain blood the red cells of which were used in the anti-A titrations from the same individual throughout the entire course of the period of observation with the result that in that particular study the red blood test cells was a variable. All tests were carried out by the same individual, who is a capable and experienced worker in this field. In many instances the titrations were checked.

In the anti-Rh titrations, the tubes were placed in a water bath at 42° C. for one hour, centrifuged at 500 r.p.m. for one minute and the sediment read both macroscopically and microscopically for agglutination. In the anti-A titrations, the tubes were allowed to stand at room temperature for one hour, centrifuged at 500 r.p.m. for one minute and the sediment read both macroscopically and microscopically for agglutination. Readings were recorded as + + + +, + + +, + +, + and ±. The last tube showing ± agglutination was established as the end point.

When labor was established the mothers were given vitamin K in the form of Synkamin,* 2.0 c.c. intravenously. At the time of delivery the cord was not clamped until pulsations had stopped. After the cord had been cut, blood was milked from the maternal end for later study. Heel puncture of the infant was carried out and capillary blood obtained for red blood cell, white blood cell, hemoglobin, icterus index and prothrombin determinations as well as for blood smears. Sections of placenta and cord were obtained for pathologic study.

The infants were observed closely during their hospital stay. During the first three or four days red blood cell and hemoglobin determinations were carried out every six hours. For the next two or three days these determinations were made twice daily, and following that once daily. Icterus index determinations were made at frequent intervals, otherwise the infants were handled as normal newborns.

The cord blood was made use of in an attempt to find Rh antibody in the fetal blood. This was tested for by both the ordinary test tube method using the serum, and by the method suggested by Carter and Loughrey¹² using the red cells. The saliva of the infant described in Case 2 was tested for the presence of A factor.

Case Reports

CASE 1.—Mrs. G. S., a 23-year-old para i, gravida iv. Wassermann reaction negative. The obstetric and transfusion histories are summarized in considerable detail as follows: In 1939 the patient was given five transfusions, the Rh type of which is unknown. She had a reaction to one of these transfusions. Her

*Parke, Davis and Company, Detroit, Mich.

first pregnancy terminated in 1943 with the delivery of a living 1,990 Gm. male infant which died the following day. Diagnosis prematurity. Rh unknown. Two more transfusions were given the patient at this time, the Rh unknown, but there was a reaction after the second transfusion.

In May, 1944, the first Rh test was done on the patient. She was found to be group A Rh negative and to have no Rh antibody in her serum (agglutinating test only). At the time of this test the patient was about four months pregnant, her expected date of confinement being Oct. 6, 1944. Her husband is group O Rh positive.

On Sept. 18, 1944, Rh blocking antibody (Wiener¹³) was found in the maternal serum. However, this was the first time the blocking antibody had been tested for; the agglutinating antibody was negative. On Sept. 21, 1944, this second pregnancy terminated by midforceps delivery of a living 3,800 Gm. male infant after a 34-hour labor. The infant required resuscitation. His skin had a lemon yellow tint; the conjunctivae were icteric, as was the cord; the scrotum was very edematous; the abdomen was very distended and the skin of the abdomen showed pitting edema. A large liver was readily percussed, but the exact edge could not be palpated because of abdominal distention. The spleen was not felt. Numerous petechial hemorrhages appeared on the body and face during the first hour of life.

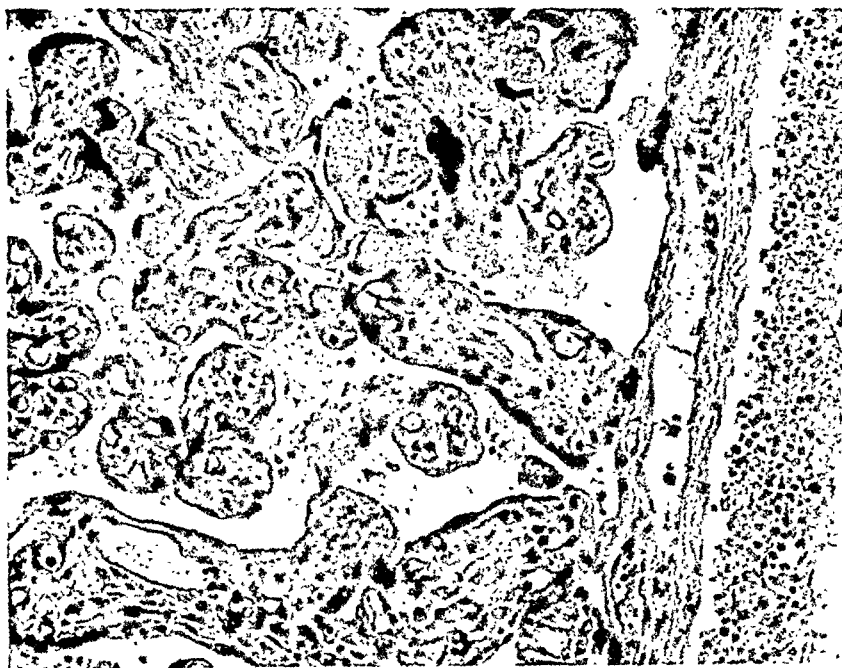


Fig. 1.—Photomicrograph of placenta from Case 1. Infant born 1944, died ten hours after birth from hemolytic disease of the newborn. Large vessel at top shows many nucleated red blood cells. The villi are thick, heavy, blunt. Stroma is heavy. ($\times 210$.)

Two hours after birth the infant was transfused with 70 c.c. of group A Rh-negative blood. Hemoglobin at the end of this transfusion was six grams. Eight hours after birth a transfusion of 50 c.c. group A Rh-negative blood was performed. Ten hours after birth the infant expired. Blood typing—group A, Rh positive.

Clinical diagnosis: Erythroblastosis fetalis.

Anatomic diagnosis following autopsy: Erythroblastosis fetalis.

Placenta: weight 860 grams. Ratio of placental weight to that of fetus 1:4.4. Cotyledons grossly were large, very smooth, pale pink color.

Pathologist's diagnosis: erythroblastotic placenta (Fig. 1).

On March 8, 1945, a test for blocking antibody in the patient's serum was negative. At this time the patient was about five weeks pregnant (her third pregnancy), the last menstrual period being Jan. 28, 1945. On May 23, 1945, the blocking antibody was again found, and this increased in amount until June 1, 1945. On June 6 the patient reported she had not felt life for four days, and on July 5 labor was induced by the use of a Voorhees bag. On July 7, the third pregnancy terminated by spontaneous delivery of a 290-Gm. macerated male fetus. Autopsy was not done. Placental weight, 300 grams. The ratio of placental weight to that of fetus was 1:1. Pathologist's report: abortion.

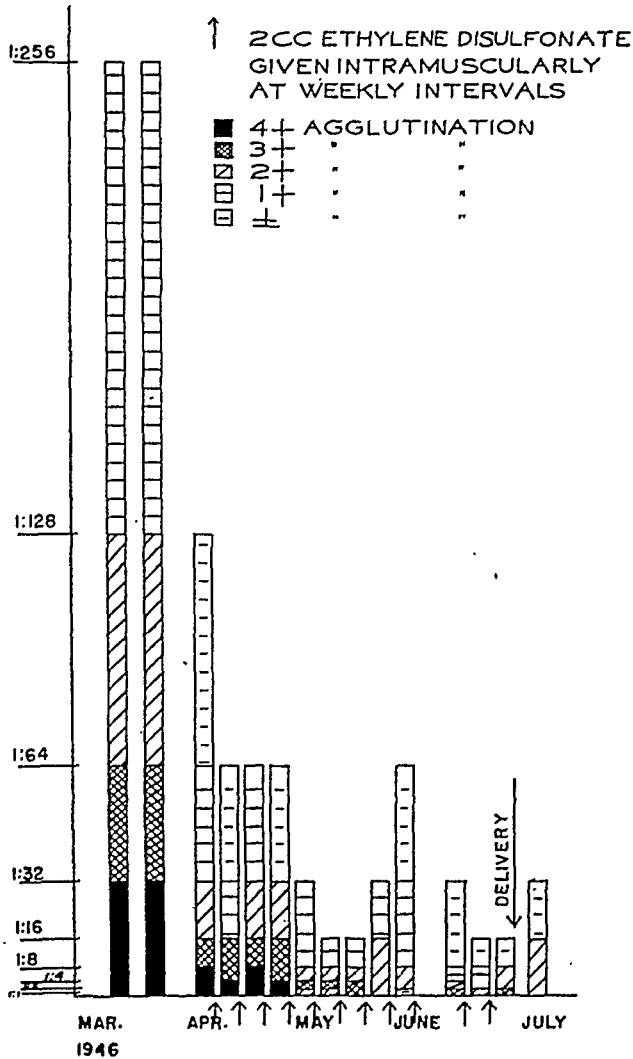


Fig. 2.—Conglutinin titrations Case 1.

On March 15, 1946, the patient reported to clinic stating that her last menstrual period had been Oct. 7, 1945. The estimated date of confinement was July 14, 1946. The Rh conglutinin titers during the course of this pregnancy are shown in Fig. 2 along with the dosages of ethylene disulfonate administered. Agglutinating antibody was never found in the serum. On June 29, 1946, the fourth pregnancy terminated by spontaneous onset of labor with delivery of a living 3,380 Gm. female after a labor of fifteen hours. Physical examination of the infant was entirely normal. The average daily blood counts are shown in Table I. The infant was group A Rh positive. No Rh antibodies were found in the cord blood. Prothrombin time 25/26 seconds.

The infant was discharged from the hospital on its tenth day of life weighing 150 Gm. above birth weight. The clinical course of the infant during its hospital stay and subsequently was entirely normal. The infant appeared only slightly icteric on its third day of life, but this entirely disappeared within two days. Placenta: weight 680 grams. Ratio of placental weight to that of fetus 1:5. Pathologist's diagnosis: normal cord and placenta (Fig. 3).

CASE 2.—Mrs. M. A., a 30-year-old para iii, gravida iv. Wassermann reaction was negative. The patient's obstetric history is summarized in Fig. 4.

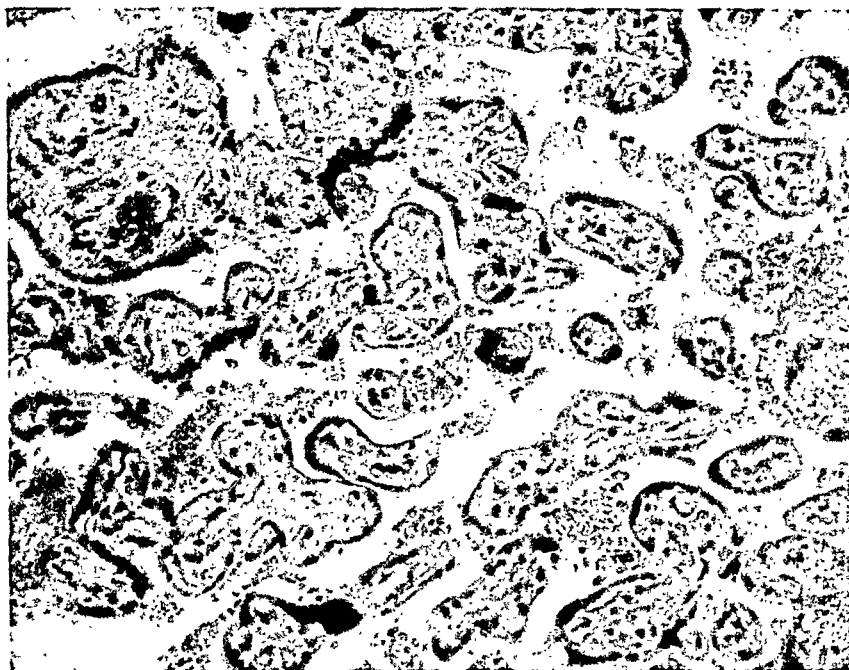


Fig. 3.—Photomicrograph of placenta from Case 1. Infant born in 1946. Normal. Mature red blood cells in small vessel near top. Normal villi. ($\times 210$.)

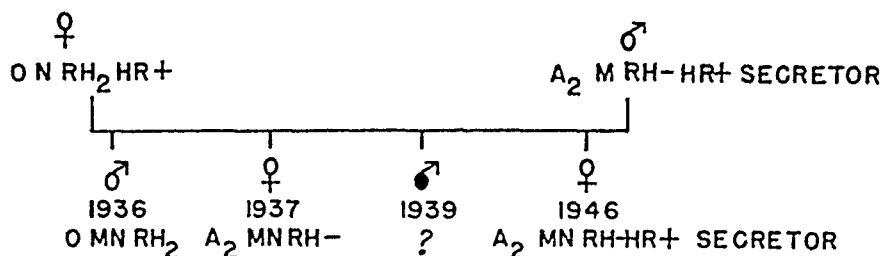


Fig. 4.—Obstetric history Case 2 (Mrs. M. A.)*

*We are indebted to Dr. Alexander S. Wiener for carrying out the Rh typing and Hr tests in this case.

The first two infants were clinically normal. The third pregnancy terminated one week past term with the delivery of a living, 2,730 Gm. male infant. It is of interest that the infant was relatively small in spite of the fact that it was delivered at full term. At the time of delivery the amniotic fluid and vernix caseosa were golden yellow colored, although the sclerae were not icteric. No note was kept concerning the placenta, nor were microscopic sections of the placenta made. When the infant was twelve hours old it was noted to be icteric. The spleen and liver were enlarged. Twenty-four hours later there was no improvement in the infant's condition. The icterus index at this time was 240 units. Red blood cells, 5.90, hemoglobin, 22.0 Gm., white blood cells, 23,000. Smear showed "definite increase in erythroblasts." Infant transfused

with 100 c.c. of mother's blood without reaction. Splenectomy was considered. However, the infant continued to do poorly, and shortly after the transfusion had a convulsive seizure. These seizures became progressively more severe and frequent and the baby died fifty-three hours after birth. Clinical diagnosis: icterus gravis.

The anatomic diagnosis following autopsy included among others, "Question of erythroblastosis fetalis." The pathologist makes a further note: "N. B.

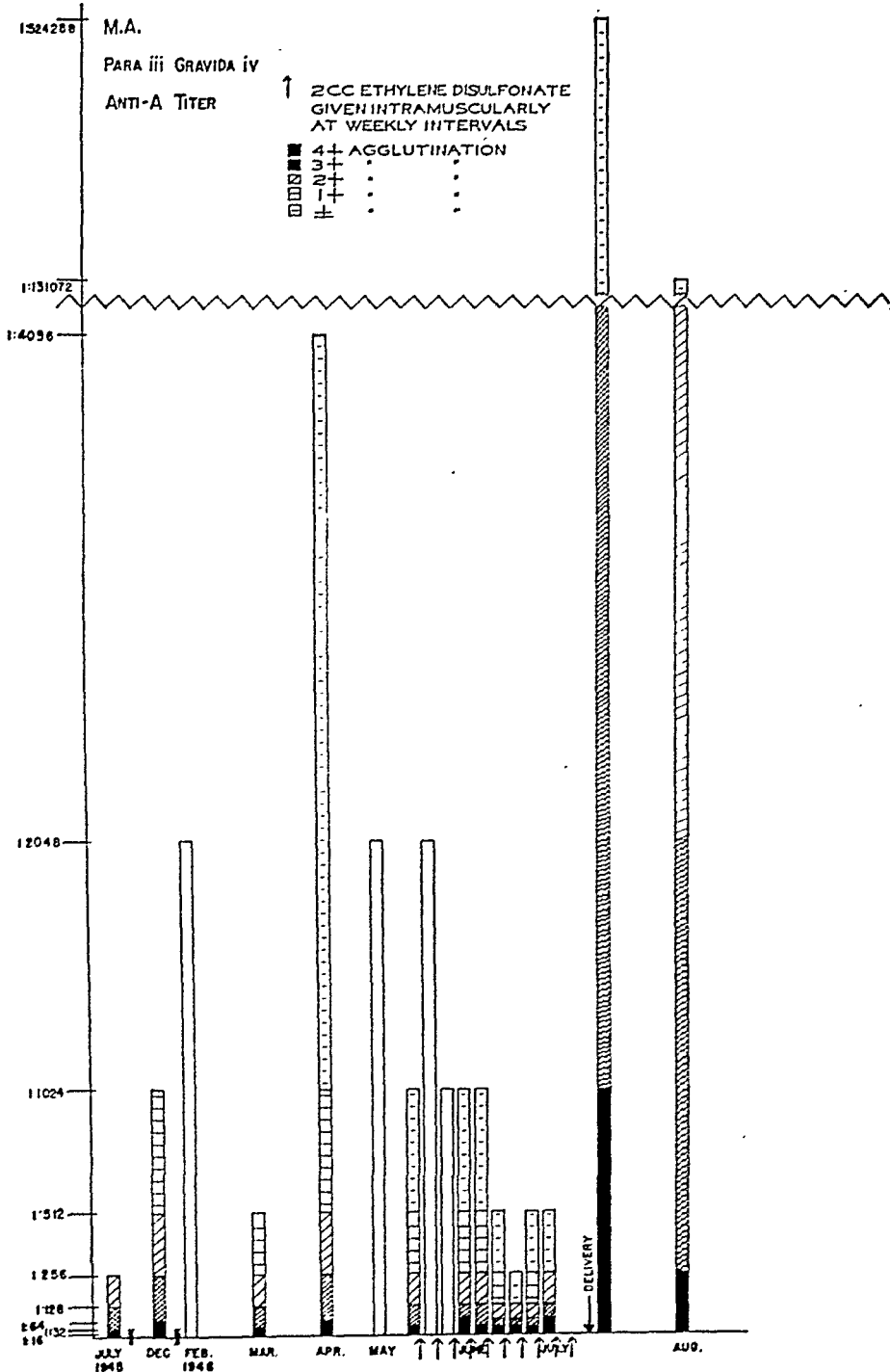


Fig. 5.—Anti-A titrations Case 2.

TABLE I. COMPARISON OF BLOOD STUDIES, OF THE THREE INFANTS DISCUSSED, WITH NORMAL VALUES AS PRESENTED BY CHUINARD, OSGOOD, AND ELLIS¹⁵

| DAYS | AVERAGE RED BLOOD CELLS (GIRLS) | | | | AVERAGE HEMOGLOBIN (GIRLS) | | | |
|------|------------------------------------|--------|--------|--------|-------------------------------|--------|--------|--------|
| | NORMAL | CASE 1 | CASE 2 | CASE 3 | NORMAL | CASE 1 | CASE 2 | CASE 3 |
| 1 | 4.65 | 5.23 | 5.59 | 4.61 | 17.01 | 22.00 | 21.00 | 16.7 |
| 2 | 4.71 | 4.53 | 4.46 | 4.28 | 17.58 | 18.30 | 18.30 | 15.9 |
| 3 | 4.95 | 4.44 | 5.20 | 3.74 | 17.28 | 16.90 | 18.35 | 15.0 |
| 4 | 4.56 | 4.73 | 5.38 | 4.13 | 17.45 | 16.90 | 19.10 | 15.0 |
| 5 | 4.56 | 4.87 | 4.75 | 3.76 | 15.39 | 17.20 | 18.25 | 15.0 |
| 6 | 4.53 | 4.98 | 5.10 | 3.50 | 15.99 | 17.20 | 18.00 | 14.2 |
| 7 | 4.07 | 4.52 | 5.10 | 3.10 | 14.10 | 16.70 | 17.50 | 12.6 |
| 8 | 4.52 | 4.22 | 4.80 | 3.23 | 16.02 | 16.20 | 18.00 | 13.1 |
| 9 | 4.58 | | | 2.70 | 15.48 | | | 11.3 |
| 10 | 4.28 | | 4.95 | 3.60* | 14.88 | | 17.60 | 13.8" |
| 11 | | | | 3.30* | | | | 12.3* |
| 12 | | 4.25 | | 2.60* | | 16.60 | | 11.0* |
| 13 | | | | 3.30* | | | | 13.3* |

*Following transfusion.

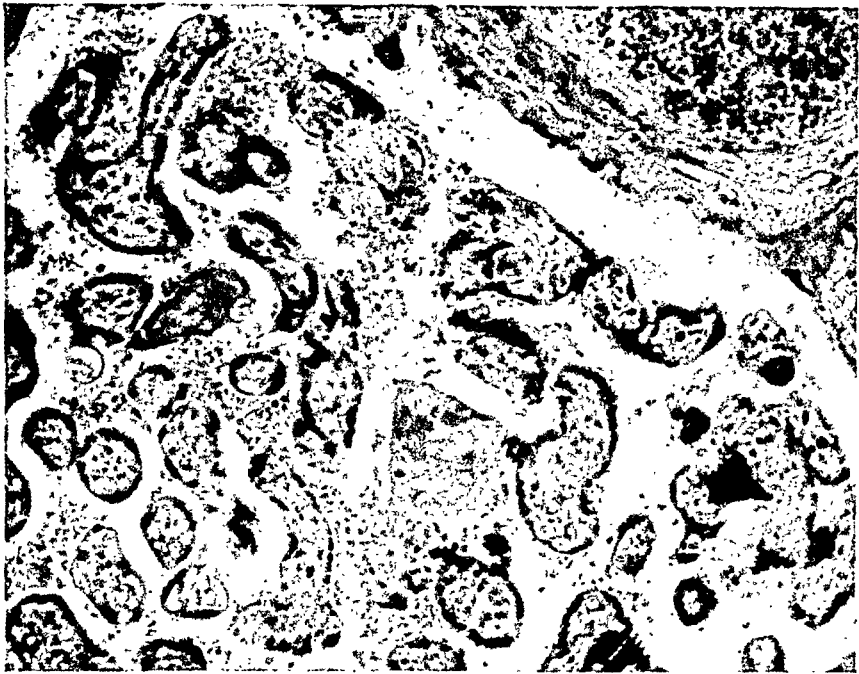


Fig. 6.—Photomicrograph of placenta from Case 2. Infant born 1946. Normal. Normal red blood cells in large vessel. Normal villi. Normal vascularity. (X210.)

The findings here are compatible with erythroblastosis fetalis, but the diagnosis must rest more on the post-mortem peripheral blood morphology."

The obstetrician made a note in the patient's chart as follows: "This patient's baby died of erythroblastosis, confirmed clinically by Dr. S. W. Clausen, professor of pediatrics, and also at autopsy. In view of the likelihood that all subsequent pregnancies may result in the same condition, it seems wise to give contraceptive advice."

In July, 1945, the patient consulted the author regarding future pregnancies. She was found to be group O Rh positive. Anti-A titer 1:256 (Fig. 5). She was seen again in December, 1945, at which time she reported her last menstrual period as Oct. 8, 1945. Her estimated date of confinement was July 15, 1946. Both A and B antibody titrations were carried out during the remainder of this patient's pregnancy. Only the anti-A titers are shown in Fig. 5, since

CASE 3.—Mrs. V. S.* A 27-year-old para iii, gravida iv. Wassermann reaction negative. The obstetric history is shown in Fig. 7.

The first two pregnancies were entirely normal, as were the infants. The expected date of delivery for the third pregnancy was Nov. 20, 1944. The pregnancy progressed in a normal manner until the patient's visit to her

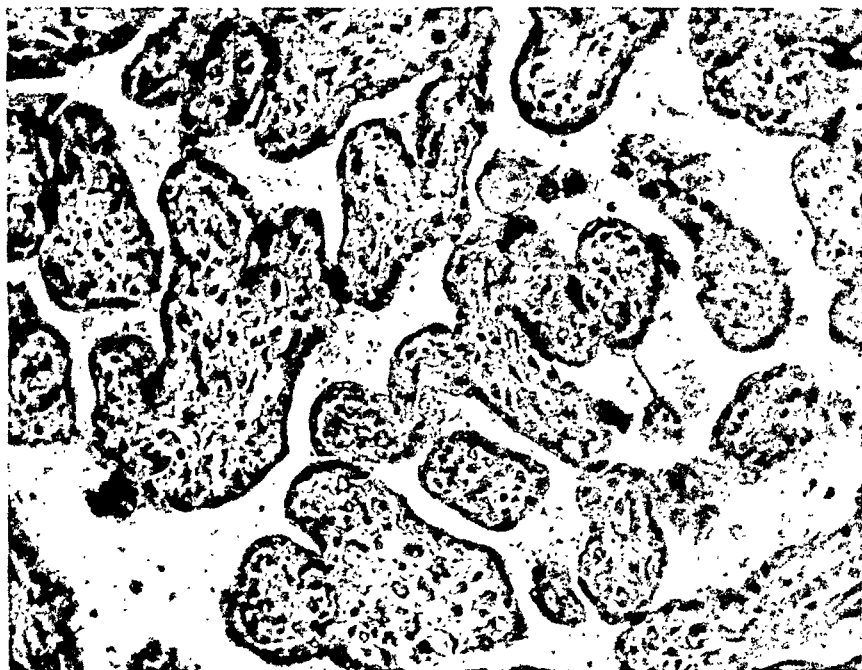


Fig. 8.—Photomicrograph of placenta from Case 3. Infant stillborn 1944. Villi large, thick, blunt. Persistence of double layered trophoblast in areas. Vascularity diminished. ($\times 210$.)

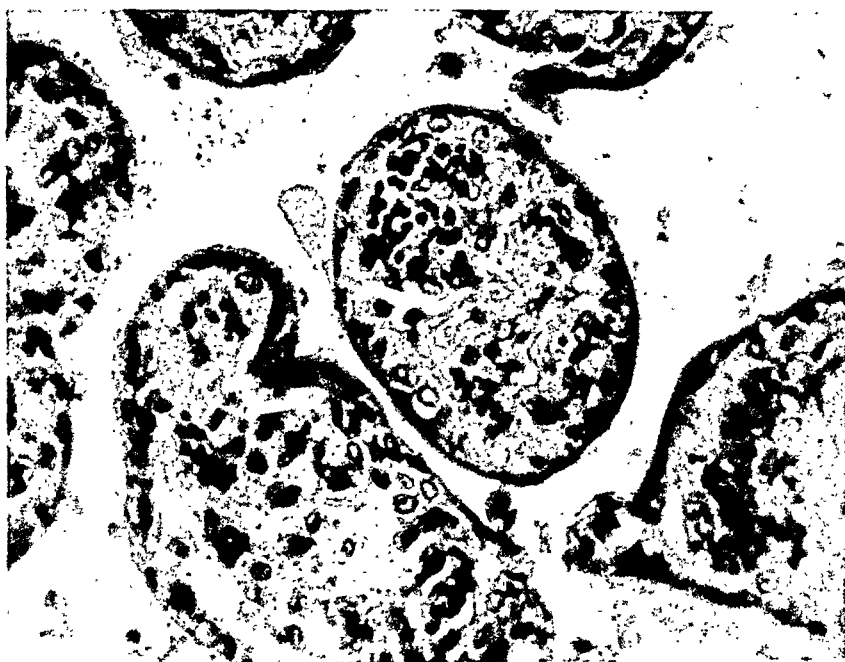


Fig. 9.—Same case as Fig. 8. Villus in center shows vessel full of nucleated red blood cells. It is large. There is persistence of Langhans' layer. Stroma is edematous. ($\times 430$.)

*This patient was delivered of her second and third pregnancies at the Genesee Hospital, Rochester, New York. We are indebted to that institution for the information we have concerning the third pregnancy, and to Dr. Jacob Epstein for allowing us to study the patient during her recent pregnancy.

obstetrician nine days before term, at which time he was unable to hear the fetal heart. Three days later the patient went into labor spontaneously and delivered a 3,370 Gm. stillborn male infant. No definite diagnosis could be made by the pathologist following autopsy because of autolysis of the organs. The protocol states, however, that there was among other things "marked edema of the subcutaneous tissues; congestion and intra-alveolar hemorrhages."¹⁰

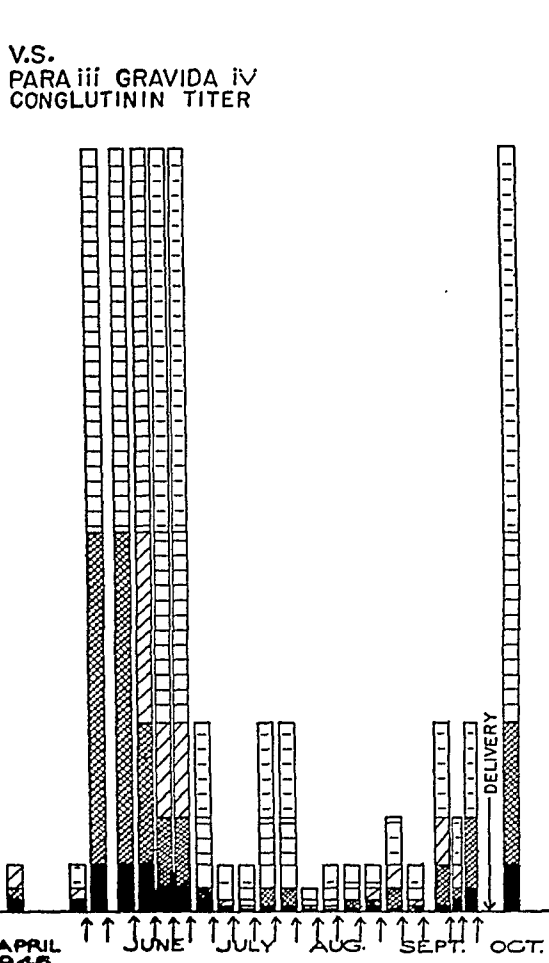


Fig. 10A.

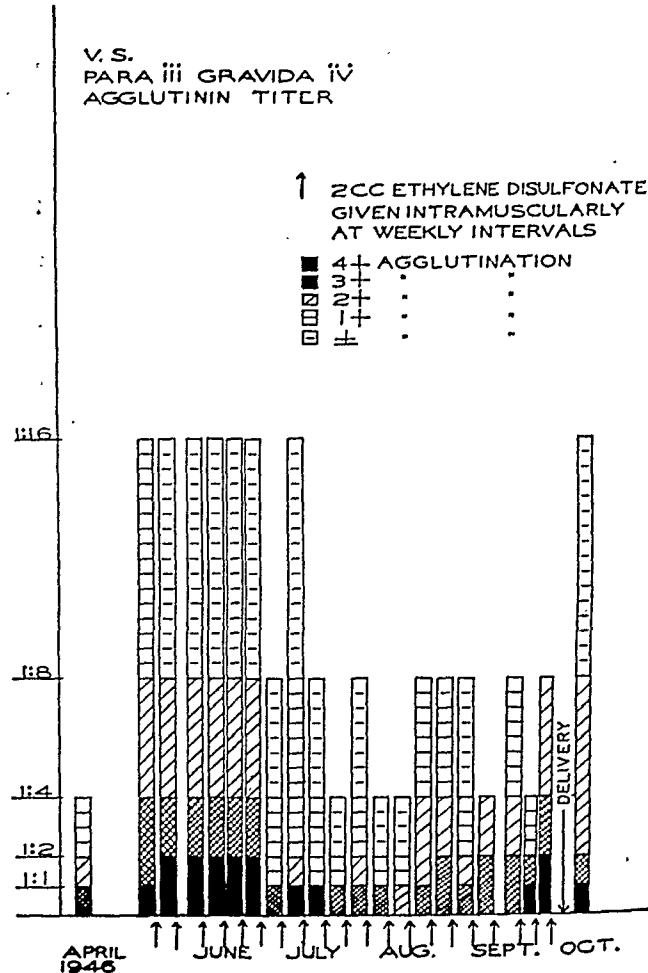


Fig. 10B.

Fig. 10.—Conglutinin and agglutinin titrations Case 3.

The pathologist felt that the microscopic picture of the placenta was "indicative of fetal erythroblastosis" (Figs. 8 and 9).

The patient consulted her obstetrician on Apr. 27, 1946 regarding her fourth pregnancy, the expected date of confinement of which was Sept. 27, 1946. The Rh-antibody titers obtained and the ethylene disulfonate dosages administered this patient during the remainder of this pregnancy are shown in Fig. 10.

On Sept. 28, 1946, medical induction of labor resulted in the spontaneous delivery of a living 3,490 Gm. female infant following a twelve-hour labor. Physical examination was entirely normal. The infant was group O, Rh positive.

*Sections of lung and kidney from this infant were sent to Dr. Edith Potter following her recent publication on the diagnosis of hemolytic disease of the newborn in the macerated fetus,¹⁴ and she reports as follows: "The presence of the large immature red cells in the lung is not as marked as in some cases, but I believe they are found in sufficient numbers to make a presumptive diagnosis of erythroblastosis. The blood within the larger vessels also shows a higher incidence of nucleated cells than is normally found. The vessels in the kidney likewise show nucleated cells in greater numbers than normal."

Cord blood revealed an Rh conglutinating antibody titer of 1:128. This had fallen to 1:64 in venous blood obtained by heel puncture on the infant's ninth day of life. In neither case was agglutinating antibody found. Only the more pertinent blood studies done on this infant are presented in Table II.

On Oct. 17, 1946, the infant's nineteenth day of life, it was discharged from the hospital weighing 520 Gm. above birth weight. The clinical course of the infant during its hospital stay was typically one of hemolytic disease of the newborn. At the time of discharge, the baby appeared to be entirely normal. Its subsequent course has been uneventful.

Placenta: weight 550 Gm. Ratio of placental weight to that of the fetus 1:6.3. Pathologist's diagnosis: Normal cord and placenta (Fig. 11).



Fig. 11.—Photomicrograph of placenta from Case 3. Infant born 1946. Normal. Placenta normal. (X210.)

Discussion

The author has attempted to prove that in each of the three cases presented the patient had, prior to the present study, given birth to one or more infants suffering from hemolytic disease of the newborn. To this end extensive case histories and photomicrographs of placentas have been presented. If it is conceded by the reader that in each case a history of hemolytic disease of the newborn exists, then he must likewise concede that all subsequent pregnancies should result in the delivery of an infant with hemolytic disease of the newborn, provided certain criteria are fulfilled. If this is not so, then we must abandon our entire concept of the etiology of hemolytic disease of the newborn. In Cases 1 and 3, in order for this to happen, it would be necessary that subsequent infants be Rh positive. In Case 2 it would be necessary that the infant belong to group A and that the mother again be sensitized to the A factor, as she was in her previous pregnancy. In each instance, it has been demonstrated that these criteria have been fulfilled. One can conclude, therefore, that in each case, the most recent pregnancy should have resulted in the birth of a

baby suffering from hemolytic disease of the newborn. That this did not happen is obvious from the results presented. The infants in Cases 1 and 2 were clinically normal. In Case 3, the infant very obviously had hemolytic disease, but in a form amenable to treatment and mild enough that it survived following transfusion. This occurred, in spite of the fact that the previous pregnancy of this patient resulted in the birth of a stillborn, possibly hydropic infant.

In Cases 1 and 2 there was no evidence clinically that the infants were not normal. Physical examination was entirely normal at birth and remained so throughout the period of observation. In both instances there was possibly slight icterus on the third and fourth days of life, respectively, but no more than one sees frequently and interprets as a very mild physiologic jaundice. In each instance this very slight icterus was gone within two days. In both cases the infants took their feedings well, gained satisfactorily, and were discharged from the hospital above birth weight.

Table I lists the daily average red blood cell and hemoglobin values of all infants and compares them with normal values as published by Chuinard, Osgood, and Ellis.¹⁵ In Cases 1 and 2 the initial levels for both red blood cell and hemoglobin were higher than normal, possibly due to the fact that the cords were not clamped until pulsations had stopped, and there was consequently a drop in the levels on the second day in each case. From this point on, however, the values were equally high or higher than the normal values listed.

In case three the findings were not as dramatic, but the results were equally satisfactory, in that this patient now has a normal healthy baby, when it could rightfully be expected that she should have delivered another stillborn and probably hydropic infant. The baby in question began to show slight icterus on its third day of life, and by the fourth day was definitely icteric. At no time was the liver or spleen palpable. The infant appeared well and took its feedings satisfactorily resulting in a good weight gain so that at the time of discharge from the hospital it was far above birth weight. The average daily red blood cell and hemoglobin levels of this infant (Tables I and II) gradually fell until on the ninth day of life, transfusion seemed to be indicated. It was then found necessary to give the infant a total of 260 c.c. of Rh-negative blood before a satisfactory level was maintained.

From the foregoing, one can deduce that the three infants under discussion should have had hemolytic disease of the newborn, but that only one of them did suffer from that disease, and that one only in a form mild enough that it was entirely amenable to transfusion therapy.

It is essential now that we review the antenatal care of the patients in these three cases. This consisted of repeated intramuscular injections of ethylene disulfonate in a dilution of 1:10⁻¹⁵ in distilled water, along with close observation of the titer of Rh antibody and alpha agglutinin. From Figs. 2, 5, and 10, one can see that in each instance the offending antibody titer fell from relatively high levels to relatively low ones. Case 3 differs from the first two in this regard in that the level did not remain low, but tended to rise, not only in the total number of test tubes in which agglutination was detectable, but in the degree of

agglutination present in each tube. This would seem to be significant, since the patient in this case delivered an infant with hemolytic disease of the newborn, whereas the patients in the first two cases delivered normal infants.

In a large series of cases in which we have had the opportunity to follow antibody titers during pregnancy, we have never observed a fall in titer, as was noted in these cases, except when the infant dies in utero. Our experience has been that the level either remains static or rises gradually. This has been the experience of others.¹⁶

What, then, brought about this fall? It must be one of two things; either ethylene disulfonate or distilled water. It does not seem possible that the minute quantities of ethylene disulfonate given could have any effect upon the antibody producing mechanism of the body. How could the distilled water do this? One possible answer is that as the result of the injection of such an unphysiologic solution into muscle tissue, there is a certain amount of tissue damage. This in turn could cause the liberation of an "x" substance which when picked up by the blood stream would neutralize all the circulating antibody, and thus bring about a fall in antibody level. Another possibility would be that this "x" substance would attract all antibodies to the site of injury, and likewise deplete the serum titers. Repeated injections of the offending agent would tend to make the process continuous.

We have observed as have others that the absolute level of titration of the Rh antibody bears little or no relationship to the severity of the disease in the newborn. In view of the present observations, it is felt now that that statement is only a partial truth. We believe now that the total antibody level when it is coupled with the amount of agglutination per test tube may be of definite help in prognosticating the seriousness of the disease in the newborn. For example, a serum carrying a titer of 1:64 in which only the first tube shows 4+ agglutination is not as potent a serum as one carrying a titer of 1:64 in which five of the tubes show 4+ agglutination. Figs. 1 and 10 illustrate this point. The technique of performing the titration tests must, of course, be kept uniform in all respects. In addition, it would seem that the length of time the patient carries a high titer of antibody is more important than the height of the titer of the antibody. So that when one attempts to prognosticate the severity of hemolytic disease of the newborn, he should consider three factors; (1) the length of time before term that antibody appears in the maternal serum, (2) absolute height of antibody, and (3) degree of agglutination per test tube noted when titration is being carried out. This proposition is based on the fact that in Cases 1 and 2 the high titer and high degree of agglutination (4+ and 3+), were carried for only a relatively short time, while in Case 3, although the high titers were present only a relatively short time, still the degree of agglutination per tube (4+ and 3+) remained elevated for a considerably longer period. When reviewing the individual tube agglutination for Case 2 (Fig. 5), it must be kept in mind that the alpha agglutinin is a natural one for this patient and that its usual titer of 1:256 is illustrated in the first column to the left of the figure. Apparently it is not possible to reduce the total titer or degree of agglutination per tube below those values observed in the pre-pregnant state.

The conclusion, then, seems justified that as a result of the intramuscular injection, as given, two infants were spared from hemolytic disease of the newborn, while the third had the disease in a milder form than would normally have been expected.

No other patients have been handled in the manner described. However, further studies are being made on the use of distilled water in this connection.

It is of interest to note that no marked change in antibody level was apparent until four to six injections had been given. The significance of this is not clear. It is also of interest that in each case there was a rise in antibody level on the eighth to tenth postpartum day. This reaction has been described by others. It is especially marked in Case 2 (Fig. 5).

In Case 3 when it was definitely established that the antibody was rising again as the patient approached term an attempt was made to arrest this by increasing the frequency of injections, but to no avail. It is entirely possible that had labor been induced four to six weeks before term, an entirely healthy, though premature infant would have resulted. Instead, the patient was allowed to go to full term at which time induction of labor was carried out.

It is interesting to note that in Case 2, although the infant belonged to group A, the cord blood carried an anti-A titer of 1:64. In Case 3 the Rh agglutinating antibody in cord blood was 1:128, and still remained high in venous blood drawn from the infant nine days later.

Case 2 is one more to add to the list of hemolytic disease of the newborn due to A-O or B-O incompatibility. Boorman, Dodd, and Mollison,¹⁷ La Vake,¹⁸ Polayes,¹⁹ and Wiener²⁰ have reported other cases. This is similar to some reported by Wiener in that the infant was a secretor, as they were in some of his cases.

It should be stated that very rarely will one find Rh antibodies in the maternal serum in goodly amounts only to have that patient later deliver a healthy Rh-positive infant. In fact the author has reported two such cases.⁶ In neither case, however, had the patient previously delivered an infant suffering from hemolytic disease nor had this been so in the other similar cases reported.^{21, 22} It is on this fundamental point that these cases differ from those described in this presentation.

Summary

Three cases are presented in which an attempt was made to prevent hemolytic disease of the newborn by means of intramuscular injections of ethylene disulfonate in distilled water into the mother ante partum.

In two of the cases normal infants were born while in the third case the infant suffered from hemolytic disease.

It is suggested that some nonspecific tissue reaction may bring about a lowering of the serum antibody level, and thus prevent or modify the disease in the newborn.

A more suitable plan for aiding in the prognostication of hemolytic disease of the newborn is outlined.

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A STUDY OF TWO TRANSFUSION DEATHS DUE TO Rh INCOMPATIBILITY

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SINCE the discovery of the Rh antigen in 1940 by Landsteiner and Wiener, the medical profession has become acutely aware of the importance of this factor in hemolytic disease of the newborn. Only in recent years, however, has the significance of the Rh antigen in transfusion reactions been appreciated. Much has been written concerning the need of Rh compatibility tests prior to transfusion with whole blood, and the necessity for employing Rh-negative blood in transfusing Rh-negative individuals. Yet, little information is available as to methods of therapy once a transfusion has been given with incompatible blood and a reaction occurs.

It is the purpose of this paper to report two deaths attributed to transfusion with incompatible Rh blood. The first death occurred in June, 1944, prior to the development of a definite clinic policy concerning the Rh antigen at the New York Lying-In Hospital, and was the stimulus for its inauguration in August of the same year. Cole has reported in detail the development of this policy with respect to the precautionary and investigatory procedures now employed. The second death occurred in 1945, attributed to an error in the Rh typing.

Transfusion Deaths Due to Incompatible Rh Blood

CASE 1.—The patient was a 32-year-old para iii, gravida vi, who was admitted to the obstetric service in 1944 at seven months gestation with a history of antepartum bleeding. Her obstetric history revealed one spontaneous abortion and three normal deliveries prior to the delivery of a deadborn, macerated, erythroblastotic (?) fetus at six months in 1940. When first examined in the hospital, the fetal heart could not be heard, and a sterile vaginal examination four days later showed the cervix to be three centimeters dilated with bulging membranes. The membranes were ruptured, no placenta was identified, but labor did not ensue. Because of continued bleeding, operative intervention was decided upon. Re-examination revealed the presence of a marginal placenta previa with the cervix five centimeters dilated. An internal podalic version, breech extraction, and manual removal of the placenta were performed. The infant was a 750 Gm. macerated male. During the operation the patient suffered a blood loss of 800 c.c., and a transfusion of supposedly compatible blood was given. Shortly after the transfusion was completed a reaction occurred which was characterized by chills, fever to 39.2° C., and shock. On the day following the transfusion there was an icteric tint to the sclera and skin, and it was noted that the patient had not voided since delivery. Catheterization yielded but 10 c.c. of urine. Determination of the patient's Rh type showed her to be Rh negative, while the donor was Rh positive.

The decision was made to alkalinize the patient and force fluids in the form of hypertonic glucose by mouth and by vein in an attempt to stimulate the kidneys both by massive hydration and hyperglycemia. Accordingly, the intravenous intake included 3,050 c.c. of 20 per cent glucose supplemented with 50 per cent glucose and M/6 lactate to maintain urine alkalinity. The blood nonprotein nitrogen was recorded as 78.4 mg. per cent. Examination of the urine failed to demonstrate hemoglobin or red cells. On the third post-transfusion day (hereafter to be referred to as PT day) the output was only 77 c.c. despite an intravenous intake of 3,500 cubic centimeters. Vasodilators in the form of aminophylline and caffeine were administered with no demonstrable effect. As a result of the daily use of M/6 lactate the carbon dioxide combining power of the blood rose to 90+ volumes per cent and it was discontinued. By now the patient was clinically worse. She was restless, nauseated, and drowsy. All oral feedings and fluids were promptly expelled, so that nutrition had to be maintained by parenteral feedings. An oxygen tent relieved the patient greatly.

On the fifth PT day the output had risen to 120 c.c., with an intake of 2,000 c.c. Edema of the face and extremities was marked, although the lungs were clear. Intravenous calcium chloride was administered to combat the alkalosis. By the eighth PT day the output had risen to 445 c.c., although the nonprotein nitrogen was now 114 mg. per cent. Clinically, the patient was critically ill. Generalized edema was marked; fine moist râles were heard at the bases, as well as coarse rhonchi through the lung fields; the breath was typical of nitrogen retention; and the patient was semicomatose but afebrile. As a final resort, intravenous sucrose was employed to stimulate the kidneys, without beneficial results being observed.

The next day (PT nine) the temperature rose to 38.4° C. and penicillin was started. It was the impression that the patient had a terminal pneumonia with respirations labored and shallow. The urinary output had increased to 620 c.c. In the early morning of the tenth PT day the patient went into extremis and expired. Blood chemistries drawn immediately prior to death revealed a nonprotein nitrogen of 159 mg. per cent, in spite of the steadily increasing output.

Autopsy showed that all the body cavities were partially filled with fluid. The right pleural cavity contained 500 c.c. of straw-colored fluid and the left, 250 c.c. The tissues were markedly edematous. Grossly, the lungs showed the presence of multiple areas of consolidation with large amounts of expressible fluid in the alveoli and bronchioles. The right and left kidneys weighed 300 and 325 Gm., respectively, and were larger than normal. The capsules stripped easily, exposing a pale gray, smooth cortical surface with scattered punctate areas of hemorrhage. The cut surfaces revealed a well-differentiated medullary area with scattered hemorrhages present throughout the cortices. Microscopically, the tubules in the upper medullary region were found to contain some blood cells and hemoglobin casts. Throughout the stroma of the kidney numerous lymphocytes and scattered neutrophils were present. Bowman's capsule surrounding many of the glomeruli was distended and filled with some pink precipitate.

The intake, output, and changes in the blood chemistry are tabulated in Table I.

Nonprotein Nitrogen: Two days following the transfusion the nonprotein nitrogen was elevated to 78 mg. per cent. Despite fluid therapy and an increasing urinary output, the nonprotein nitrogen slowly rose to 160 mg. per cent by the day of death. Similarly, the blood urea nitrogen showed a like pattern, rising from 63 mg. per cent to 87 mg. per cent.

TABLE I. LABORATORY STUDIES OF FIRST PATIENT DYING FROM A TRANSFUSION OF INCOMPATIBLE RH BLOOD

| PT DAY | B.U.N. | SUGAR | CO ₂ | PRO- TEIN | N.P.N. | URIC ACID | HEMO- GLOBIN | OUTPUT | INTAKE |
|-----------|--------|-------|-----------------|--------------|--------|--------------|-----------------|--------|--------|
| 1 | -- | --- | -- | -- | -- | --- | 8.5 | 0 | 3,400 |
| 2 | -- | 450 | 52 | -- | 78 | 6.0 | 6.0 | 50 | 3,050 |
| 3 | 63 | --- | 90+ | -- | 77 | 9.1 | -- | 77 | 3,500 |
| 4 | 68 | --- | 90+ | -- | 79 | 9.2 | -- | 100 | 2,000 |
| 5 | -- | --- | -- | -- | -- | --- | 6.0 | 120 | 1,900 |
| 6 | 73 | --- | 84 | -- | 100 | 16.4 | -- | 125 | 3,000 |
| 7 | 77 | --- | 80 | -- | 94 | 14.3 | -- | 170 | 2,000 |
| 8 | -- | --- | 60 | -- | 103 | 14.6 | -- | 445 | 3,050 |
| 9 | 87 | 140 | 66 | 4.8 | 115 | 15.8 | -- | 620 | 60 |
| 10 | -- | --- | -- | -- | 160 | 17.7 | -- | --- | --- |

Carbon Dioxide Combining Power: Three hours prior to transfusion the patient received 3 Gm. of sodium bicarbonate by mouth. On the first PT day she received a total of 8 Gm. of oral sodium bicarbonate and 1,000 c.c. of intravenous M/6 lactate; and on PT day two 12 Gm. of oral bicarbonate of soda, and 2,000 c.c. of intravenous M/6 lactate were given. At that point the CO₂ combining power was found to be 90+ volumes per cent. Alkalinization was then abandoned, and all fluids thereafter were either 20 per cent or 50 per cent glucose. By PT day seven the CO₂ combining power was still 80 volumes per cent, so calcium chloride (10 c.c. of a 5 per cent solution) was administered twice that day. Subsequent readings were within normal range. Clinically, there were no signs of the marked alkalosis.

Uric Acid: A rise in the uric acid value occurred which more or less paralleled the rise in nonprotein nitrogen.

Water Balance: On admission to the hospital the patient weighed 58.8 kilograms. Delivery resulted in the loss of approximately 3.0 kilograms of weight,* yet at autopsy the patient weighed 60.0 kilograms. Thus, the patient gained approximately 4.2 kilograms while she was in the hospital, the majority of which was presumably represented by retained fluid.

Urine: Despite the marked alkalosis as exhibited by blood studies, the urine pH never exceeded 7.75, the usual pH being in the vicinity of 7.5. Repeated microscopic examinations failed to show the presence of red cells or cellular debris. The output steadily increased from 0.0 on PT one to 620 c.c. the day before death. The urine was consistently amber in color and usually clear, although on several occasions slight turbidity was noted.

Comment.—It is apparent in this case that the renal shutdown occurred as the result of an Rh-negative individual being transfused with Rh-positive blood, and that the accident would have been avoided had the patient been Rh typed prior to transfusion. The patient had been sensitized by previous pregnancies, for she had no history of previous transfusion therapy. The oliguria appeared immediately. The treatment consisted of hydration and alkalization. Despite a CO₂ combining power of 90+ volumes per cent, there was no diuresis, nor did the urine become markedly alkaline. The cause of death was probably the massive terminal pulmonary infection. Pulmonary edema was probably no more than a secondary cause, for the greatest amount of retained fluid at death could not have been more than 4.2 kilograms. It is unlikely that this small volume could produce primary pulmonary edema. The kidney lesions were typical of transfusion reaction kidneys wherein considerable difficulty is experienced in locating lesions or casts. The greater part of the kidney parenchyma appeared normal.

CASE 2.—The patient was a 33-year-old, para iii, gravida iv, who was admitted to the obstetric service prior to the onset of labor. The past obstetric

*Fetus, 760 Gm.; blood, 800 c.c.; amniotic fluid, 1,000 c.c.; and placenta, 410 Gm.

history revealed that she had had three normal full-term deliveries. There was no positive history of hemolytic disease, although the last infant, born in 1944, became slightly jaundiced twenty-four hours after birth.

In the present pregnancy the patient was registered late in the thirty-fifth week of gestation in December, 1945. The initial examination was unremarkable; her blood was typed as group A and Rh positive. An anemia was present which did not respond to the usual therapy, so that admission to the hospital in the thirty-ninth week of pregnancy was advised. On admission to the hospital she was found to have a hemoglobin of 8.0 Gm. and a volume of 30 mm. Thus, on the following day a transfusion of 500 c.c. of group A, Rh positive, supposedly compatible blood was administered. There was no reaction until approximately two hours after the discontinuance of the transfusion, at which time the patient complained of chilly sensation, became nauseated, and vomited. Soon after this she began to talk incoherently and her face became markedly flushed. No icterus was demonstrable. Morphine and atropine were given, and shortly afterwards an infusion of M/6 lactate was started as well as oral bicarbonate of soda.

On the evening of the first PT day 20 c.c. of dark brown urine was passed which was guaiac positive for blood. By the second PT day the patient had passed a total of 70 c.c. of urine. The blood bank then rechecked the Rh of the patient and found her, contrary to their initial report, to be Rh negative. The patient was placed in an oxygen tent and local heat was applied externally to the kidney areas. Intravenous fluids in the form of 10 per cent and 50 per cent glucose were started. Aminophylline (0.5 Gm.) was given at three-hour intervals. It was felt that on this regimen diuresis might be facilitated if the blood sugar could be elevated to such a point as to cause spillage of sugar, carrying a corresponding amount of water with it through the kidney tubules, thus washing the tubules free of any possible obstructing casts or cellular debris. In view of the pronounced alkalosis exhibited in Case 1, as well as the marked edema, the sodium ion was restricted so as to minimize the storage of fluid in the extracellular compartment. Hypertonic glucose in distilled water, 6,350 c.c., was administered intravenously over a twenty-four period, and only 170 c.c. of urine was obtained. The blood sugar rose to 223 mg., far below a good renal spillage threshold. On PT day four the urine obtained was four-plus for sugar, so that maximum diuresis from glucose therapy was being achieved, yet the output was only 73 cubic centimeters.

A celiac ganglion block was performed in an attempt to eliminate any possible spasm of the renal vessels, if spasm be present, and possibly increase the blood flow through the kidneys. This procedure failed to produce any increased urinary function. On the fifth PT day it was decided to attempt induction of labor so as to utilize the diuretic phenomenon seen in the early postpartum period. The patient delivered precipitately after two and one-half hours of labor. The infant was a living, normal, 3,580 Gm. female with no signs of hemolytic disease. The infant was found to be Rh positive. The output on that day, despite delivery, was only 21 c.c., the intake 2,500 c.c. By now clinical edema was demonstrable in the extremities, face, and over the sacrum.

By the seventh PT day mercurial diuretics were employed in view of the alarmingly low output, 20 to 30 c.c. per day, as well as a steadily rising non-protein nitrogen, now elevated to 101. Mercupurin was given in two repeated doses of 1 c.c. each. Catheterization following each injection yielded 12 c.c. and 2 c.c. of urine, respectively. The edema was marked, although, except for an inconstant rhonchus, the lungs were quite clear. There was obvious clouding of the sensorium, and a rather marked diarrhea was present. Despite the employment of mercupurin, the total output for the twenty-four hour period

was only 47 c.c. Mercuhydrin was given in two doses with no demonstrable effect. The blood chlorides had dropped to 391 mg. per cent, so on PT day eleven, 4.5 to 13.0 grams of salt a day were given with the parenteral glucose of 2,500 to 3,000 c.c. a day. Peculiarly enough, the day the salt was added the output increased from 108 c.c. to 908 c.c. Penicillin was started prophylactically in an attempt to prevent the pneumonia previously observed in Case 1.

Clinically, the patient showed marked improvement now. By the thirteenth PT day the urinary output was 3,150 c.c., excelling her intake. The urine had a specific gravity of 1.009 and contained 156 mg. per cent of urea. It was evident that the kidneys were recovering, for their ability to excrete urea had returned, and the nonprotein nitrogen fell from 130 to 111 mg. per cent. The patient could take feedings by mouth and could tolerate being out of the oxygen tent for several hours at a time. The stupor and semicoma had disappeared. Edema was difficult to demonstrate, and examination of the lungs showed them to be clear.

On the fifteenth PT day the clinical picture suddenly and dramatically changed. The pulse became rapid and irregular. Respirations were shallow and rapid. The patient became apprehensive, restless, and finally irrational. Examination of the chest revealed the presence of numerous adventitious sounds, râles and rhonchi throughout. Cyanosis appeared despite the oxygen tent. Pulmonary edema and congestion were obvious and her condition became rapidly grave. Therapy consisted of oxygen by face mask, aminophylline, papaverine, and an attempted but unsuccessful phlebotomy. The patient's course was rapidly downhill and she expired in a few hours.

At autopsy there was a bilateral pleural effusion, 300 c.c. on the right, and 150 c.c. on the left. The lungs were edematous and contained massive areas of consolidation typical of terminal pneumonia. The kidneys were larger than normal, weighing 250 Gm. each. The capsules stripped with ease. Numerous minute, pinpoint spots were seen on the surface, the general appearance being pale and somewhat amber. Microscopically, the kidneys showed a few areas with hemoglobin casts, cellular debris, and unrecognizable coagulum, primarily in the convoluted and collecting tubules. The majority of the kidney parenchyma showed little if any pathologic changes.

Table II shows the blood changes and a record of the patient's intake and output.

TABLE II. LABORATORY STUDIES OF A SECOND PATIENT DYING FROM A TRANSFUSION OF INCOMPATIBLE RH BLOOD

| PT. DAY | B.U.N. | SUGAR | CO ₂ | PRO- TEIN | N.P.N. | URIC ACID | BLOOD CL. | HEMO- GLOBIN | CELL VOL- UME | I.V. IN- TAKE | TOTAL IN- TAKE | URINE OUTPUT |
|------------|--------|-------|-----------------|--------------|--------|--------------|--------------|-----------------|---------------------|---------------------|----------------------|-----------------|
| 1 | -- | --- | -- | -- | -- | --- | -- | -- | -- | --- | --- | 20 |
| 2 | 84 | --- | 59 | -- | -- | --- | -- | 10.0 | -- | 2,160 | 5,210 | 40 |
| 3 | 66 | 223 | 62 | 4.4 | 82 | 7.4 | 479 | -- | 40 | 6,350 | 6,450 | 170 |
| 4 | 65 | 133 | 60 | 5.3 | 84 | 8.9 | 469 | -- | -- | 2,450 | 2,685 | 73 |
| 5 | 69 | 190 | 49 | 5.5 | 81 | 10.6 | 446 | 6.5 | 21 | 2,335 | 3,135 | 21 |
| 6 | 69 | 190 | 57 | 5.3 | 88 | 11.1 | -- | -- | 31 | 1,500 | 2,360 | 31 |
| 7 | 86 | 89 | 51 | 5.1 | 101 | 10.9 | 423 | 6.2 | -- | 3,500 | 3,640 | 47 |
| 8 | 89 | --- | 45 | -- | 102 | 13.1 | 399 | -- | 19 | 3,500 | 3,980 | 38 |
| 9 | -- | --- | -- | -- | --- | --- | -- | -- | -- | 2,300 | 2,640 | 105 |
| 10 | 101 | 77 | 33 | 4.8 | 130 | 13.1 | 391 | -- | 21 | 3,000 | 4,970 | 108 |
| 11 | 100 | 79 | 41 | -- | 126 | 12.0 | 376 | -- | -- | 2,500 | 3,705 | 908 |
| 12 | 104 | 75 | 40 | 5.0 | 120 | 11.6 | 385 | 5.7 | -- | 2,500 | 3,885 | 1,930 |
| 13 | 107 | --- | 45 | 5.1 | 111 | 13.6 | 396 | -- | -- | 3,150 | 4,330 | 3,150 |
| 14 | 102 | 85 | 45 | -- | 137 | 12.3 | 421 | -- | 21 | 2,500 | 4,000 | 3,850 |
| 15 | 97 | --- | 37 | -- | --- | --- | 424 | 8.0 | 21 | 2,500 | 4,150 | 4,200 |

Blood Urea Nitrogen and Nonprotein Nitrogen: On the second PT day the blood urea nitrogen was 84 mg. per cent. Slowly, throughout the next thirteen days, it steadily increased, plateauing around 100 mg. per cent during the last five days. The various procedures performer had little effect on this rise. The nonprotein nitrogen similarly rose, although the drop after diuresis had started was noticeable. Although the excretion of urea was observed from PT day eleven and on, there was no marked alteration in the nonprotein nitrogen.

Blood Sugar: It is interesting to note that, although massive glucose therapy was employed, the blood sugar was always below 100 mg. per cent but for the first five days of therapy. After 6,350 c.c. of glucose solutions, containing 1,245 Gm. of glucose, had been given, the blood sugar on PT day three was only 223 mg. per cent and the urine only two-plus for sugar. This utilization on a metabolic basis is unexplainable.

Chlorides: In order to prevent edema and storage of fluid in the extra-cellular compartment, salt was withheld. However, on PT day eleven, due to the drop in blood chloride level, salt was administered in doses of 4.5 to 13 Gm. a day.

Plasma Proteins: Each time a drop in the plasma proteins was observed 500 c.c. of pooled plasma was given. A total volume of 1,750 c.c. was necessary.

Carbon Dioxide Combining Power: On PT day two the CO₂ was 59 volumes per cent. No alkali was given until the tenth PT day in view of our experience in Case 1. On PT day ten the CO₂ fell to 33 volumes per cent, and a good response was obtained when M/6 lactate was given.

Water Balance: The admission weight was 74.1 kilograms. At delivery the patient lost about 6.0 kilograms.* At autopsy the patient weighed 85.0 kilograms. This represented a weight gain of 16.9 kilograms, all of which probably was retained fluid.

Urine: Table III shows the urine findings during the oliguria and the apparent recovery phase.

From Table III it can be seen that the large volumes of urine passed did contain the usual amounts of urea, even though the specific gravity was low. Yet with this amount of nitrogenous material being passed, the blood levels of nitrogen products still remained elevated. Also, the negative microscopic exam-

TABLE III. URINE EXAMINATIONS OF SECOND PATIENT DYING FOLLOWING TRANSFUSION OF INCOMPATIBLE Rh BLOOD

| PT DAY | COLOR | SPECIFIC GRAVITY | REACTION | ALBUMIN | SUGAR | ACET. | URINE U.N. | MICROSCOPIC |
|--------|--------|------------------|----------|---------|-------|-------|------------|-------------|
| 0 | amber | QNS | acid | 0 | ++ | 0 | -- | negative |
| 1 | brown | QNS | acid | +++ | 0 | 0 | -- | RBC, casts |
| 2 | amber | QNS | 7.0 | -- | + | -- | -- | ----- |
| 3 | ----- | QNS | -- | -- | ++++ | -- | -- | ----- |
| 4 | amber | QNS | 5.5 | -- | ++ | -- | -- | ----- |
| 5 | amber | QNS | 5.5 | -- | + | -- | -- | ----- |
| 6 | straw | QNS | 6.9 | ++ | + | -- | -- | ----- |
| 7 | yellow | QNS | 7.2 | + | + | -- | -- | ----- |
| 8 | yellow | 1.006 | -- | -- | -- | -- | -- | ----- |
| 9 | ----- | 1.005 | -- | -- | -- | -- | -- | ----- |
| 10 | cloudy | -- | 7.6 | ++ | 0 | 0 | -- | debris |
| 11 | cloudy | 1.002 | alk. | + | 0 | 0 | -- | ----- |
| 12 | cloudy | 1.002 | 7.0 | tr. | 0 | 0 | -- | negative |
| 13 | cloudy | 1.002 | 6.0 | 0 | 0 | 0 | 156 | negative |
| 14 | cloudy | 1.009 | -- | 0 | 0 | 0 | 157 | negative |
| 15 | cloudy | 1.009 | -- | 0 | 0 | 0 | 156 | negative |

*Fetus, 3580 grams; placenta, 640 grams; amniotic fluid, 1,000 grams; blood and lochia, 800 grams.

inations on these same days showed that little if any debris or casts were being removed from the kidney in the diuresis phase.

Comment.—This patient was sensitized by pregnancy, and the reaction was due to Rh incompatibility. Blood drawn on the third PT day for antititer determination showed that the "serum did not contain any blocking antibodies, and the test with serum-suspended cells was negative. Presumably this was due to the so-called negative phase of iso-immunization, and it could be expected that in a week or ten days antibodies would be demonstrable." A blood specimen drawn on PT day ten showed that the "serum was weakly positive for blocking antibodies with a questionable reaction to serum suspended cells." Another qualified examiner reported this same specimen to contain "anti-rh agglutinins of the hyperimmune type or blocking variety which is consistent with a transfusion of incompatible blood." The error in typing was due to testing serum of poor specificity employed at that time. A recheck of other patients whose Rh type had been determined with this same serum showed six additional incorrect reports.

The treatment in this case consisted chiefly of hydration with hypertonic glucose supported with mercurial diuretics, xanthine derivatives, celiac ganglion block, and evacuation of the uterus. The effect of the mercurials as a diuretic agent was unremarkable. The xanthines were ineffectual. It is apparent that the diuresis so commonly seen following delivery cannot and does not occur when urinary suppression is present. Celiac ganglion block likewise failed to alter the picture. Sodium chloride, lactate solution, and plasma were all given as supportive measures to restore and maintain the blood chemical picture as near to normal as possible. The hemoglobin was consistently low. Possible immediate and repeated transfusions of Rh-negative blood might have altered the outcome.

The cause of death was again primarily related to an overwhelming pneumonia, in spite of adequate penicillin therapy for the five days preceding death. Except for one isolated elevation to 38° C. on PT day twelve, the patient's temperature remained normal or subnormal. Pulmonary edema was present terminally and no doubt contributed greatly to the final episode, for at this time the patient was in positive water balance of 17 liters. The renal pathology cannot completely explain the sudden exodus of the patient during the apparent recovery phase of diuresis.

Reports of Similar Cases

Fifteen cases have been selected from the literature for comparison and contrast with the two transfusion reactions presented in this paper. These 17 cases may be briefly summarized in Table IV. All cases selected show proved Rh-negative recipients, and all donors except two were proved to be Rh positive. As to the two exceptions, one donor was represented by pooled red cells; the other by four transfusions of untyped Rh Blood. There was a history suggesting hemolytic disease in 12 cases, and five of the seven deaths occurred in this group. All patients belonged to either group A or group O. In only four cases was toxemia manifested. Chills and fever were the commonest symptoms oliguria the commonest sign. Hemoglobinuria occurred in eight cases, and lumbar pain in five. Vomiting was observed in four cases. In two of the cases shock and air hunger were noted. Clinical jaundice appeared in about one-half of the cases, as did also edema.

The amount of blood given was usually 500 c.c., although several cases received more. In general, those patients sensitized by previous pregnancies ap-

DEATHS DUE TO Rh INCOMPATIBILITY

TABLE IV. A SUMMARY OF SEVENTEEN CASES OF BLOOD TRANSFUSION REACTIONS RESULTING FROM Rh INCOMPATIBILITY

| Reference | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 |
|-----------------------|-----------------|-------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Age | 7 | 17 | 2 | 2 | 5 | 4 | 4 | 4 | 1 | 1 | 24 | 24 | 24 | 6 | 6 | 6 | 17 |
| Parity | 35 | 48 | 38 | 36 | 32 | 30 | 32 | 38 | 26 | 29 | 40 | 43 | 34 | 38 | 31 | 32 | 33 |
| Toxemia | 3 | 4 | 6 | 5 | 2 | 2 | 3 | 2 | 3 | 1 | 3 | 4 | 5 | 4 | 6 | 6 | 4 |
| Hemolytic disease | 0 | 0 | 0 | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Volume of transfusion | 1,000 | 900 | 500 | 100 | 1,750 | 1,075 | 1,250 | 500 | 500 | 500 | 500 | 500 | 1,500 | 200 | 250 | 500 | 500 |
| X match | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Receiving group | A | A | A | O | A | O | ? | ? | O | A | A | A | A | O | A | O | A |
| Donor group | O | A | A | O | A | O | + | + | + | + | + | + | + | + | + | + | + |
| Receiving Rh | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Donor Rh | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Reaction in hours | ? | 6 | 1 | 2/3 | ? | 1/2 | 1 | ? | ? | Im. 1/4 | 12 | ? | ? | Im. Im. | Im. | Im. | 2 |
| Lumbar pain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Chill or fever | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Vomiting | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Shock | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Oliguria | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hemoglobinuria | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Alkalinization | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Day of diuresis | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| B. U. N. | 10 | 8 | 130 | 11 | 7 | 11 | 82 | 7 | 160 | 92 | 3 | 92 | 3 | 10 | 11 | 11 | 11 |
| N. P. N. | 135 | 8 | 11 | 11 | 350 | 16 | 7 | 7 | 9 | 3 | 3 | 3 | 3 | 50 | 87 | 107 | 107 |
| On day | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Edema | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Jaundice | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| On day | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Treatment | Pl. Bl. Gl. Sa. | Cit. Sul. Gl. Sa. | Pl. Bl. Gl. Sa. | Pl. Bl. Gl. Sa. | Pl. Bl. Gl. Sa. | Pl. Bl. Gl. Sa. | Pl. Bl. Gl. Sa. | Pl. Bl. Gl. Sa. | Pl. Bl. Gl. Sa. | Pl. Bl. Gl. Sa. | Pl. Bl. Gl. Sa. | Pl. Bl. Gl. Sa. | Pl. Bl. Gl. Sa. | Pl. Bl. Gl. Sa. | Pl. Bl. Gl. Sa. | Pl. Bl. Gl. Sa. | Pl. Bl. Gl. Sa. |
| Recovery | 17 | 12 | 14 | 9 | 10 | 10 | + | + | + | + | + | + | + | + | + | + | + |
| Day of Death | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Autopsy | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |

Key: Bl. = Rh negative blood; Cit. = sodium citrate; Gl. = glucose; ML = M/6 lactate; Sa. = saline; S.B. = spinal block; Suc. = sucrose; Sul. = sodium sulfate; Rk. = reaction.

peared to have the more severe reactions, for in only two of the seven deaths was the history negative for hemolytic disease (Table IV, Cases 1 and 2).

The treatment varied greatly, although the majority of cases were treated with some form of glucose parenterally with or without saline. Alkalinization was employed in eight of the cases, and five deaths occurred in this group. Spinal block was used in one patient that recovered (Table IV, Case 9), although we used a celiac ganglion block without success in the one case. Four patients were treated with Rh-negative blood transfusion, and only one of these patients died. Resnick, 1946, reported rapid diuresis following the use of intravenous sodium sulfate, but Newton employed this same therapy without success.

Five autopsies were obtained. Darkinski, in referring to the renal lesions, states, "The cause of anuria would appear to be in the damage present in the glomerular filter. This is undoubtedly due to a nephrotoxic substance, the nature of which is not apparent or understood." Newton concluded, "There is no evidence of mechanical blockage in the tubules. Rather, a suppression of urine." We likewise feel that the renal lesions do not show mechanical blockage to be the basis for anuria and uremia. The suppression of urine must then be due to some other factor, the nature of which is not apparent to the author. The results of these cases have made us doubt the efficacy of massive glucose therapy and alkalinization.

Summary

1. Two deaths have been reported attributed to transfusion with Rh incompatible blood.
2. The details of treatment with autopsy findings have been presented.
3. Comparable cases from the literature have been reviewed and analyzed.
4. No conclusion is offered for the preferred method of therapy in transfusion reactions with uremia.

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INCIDENCE OF ISOIMMUNIZATION AMONG Rh-NEGATIVE PREGNANT WOMEN IN PUERTO RICO

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IT IS well known that Rh-negative women bearing Rh-positive children occasionally become immunized with the development of Rh antibodies. These antibodies in some instances affect the fetus, giving rise to the syndrome known as erythroblastosis fetalis.

There are two kinds of Rh antibodies: bivalent, known as agglutinins which cause in vitro visible clumping of Rh-positive red blood cells because agglutinins having two combining groups link two red cells together; and univalent, Rh antibodies also known as "blockers" or glutinins, need a third component for agglutination of the red cells to occur—this is known as conglutinin or X protein, and is present in serum or plasma.

Wiener¹ believes that there are two major disease syndromes: congenital hemolytic disease and icterus gravis, according to the type of Rh antibody present in the mother's serum.

Univalent antibodies or glutinins, being smaller, pass the placenta with greater freedom. If small amounts are present in the maternal serum the baby is born alive with anemia, or develops it shortly after birth. These babies are treated successfully with transfusions of Rh-negative blood. If large quantities of antibody are present the baby will develop extreme anemia, anoxemia, hydrops, and will be stillborn or die soon after birth. This group Wiener calls congenital hemolytic disease.

When the maternal serum contains agglutinins these bivalent antibodies, being larger, probably very seldom pass the placenta during pregnancy; at

TABLE I. BLOOD GROUP AND RH DETERMINATION OF 842 PREGNANT WOMEN

| O | A | B | AB | TOTAL | O | A | B | AB | TOTAL |
|-----|-----|----|----|-------|----|----|---|----|-------|
| 408 | 262 | 60 | 21 | 751 | 50 | 35 | 5 | 1 | 91 |

TABLE II. INCIDENCE OF ISOIMMUNIZATION TO THE RH FACTOR AMONG
91 Rh-NEGATIVE PREGNANT WOMEN

| | NO INFORMATION | NO ISOIMMUNIZATION | | ANTI-Rh AGGLUTININS |
|----------|-------------------|-----------------------|--------------|------------------------|
| | | Baby Rh pos. | Baby Rh neg. | Baby Rh pos. |
| Group O | 7 | 32 | 10 | 1 |
| Group A | 7 | 19 | 9 | - |
| Group B | 2 | - | 2 | 1 |
| Group AB | - | 1 | - | - |
| Totals | 16 | 52 | 21 | 2 |

the time of birth due to trauma they may reach the fetal circulation. The agglutination of Rh-positive infant's cells causes the formation of thrombi which leads to a series of symptoms resulting from damage to many organs. These children usually die, but, if they survive, permanent damage may result such as mental deficiency and cirrhosis of the liver. The name *icterus gravis* is applied to this group.

In order as to determine the incidence of iso-immunization among Rh-negative women in Puerto Rico and of congenital hemolytic disease and *icterus gravis* in their siblings this study was undertaken.

In a series of 842 women 91, or 10.81 per cent, were found to be Rh negative (Table I). This figure is a little higher than the one previously reported by me² (10.06 per cent) in a study of Rh types among white Puerto Ricans; as only standard anti-Rh₀ serum was used in performing the Rh determinations reported in this work, a very small percentage of Rh-positive women belonging to types Rh' and Rh'' may have been classified as Rh negative. The distribution of the four blood groups was as follows: 54.39 per cent, group O; 35.27 per cent, group A; 7.72 per cent, group B; and 2.61 per cent, group AB.

The bloods from the Rh-negative women were studied within seventy-two hours after delivery (in most instances within twenty-four hours) to determine whether Rh antibodies resulting from iso-immunization were present.

The mother's serum was tested with known O Rh-positive (type Rh₁Rh₂) and O Rh-negative red blood cells; the baby's cells were included in the tests if he belonged to the same blood group as the mother, or to group O.

In the agglutination tests, the Levine test tube technique was employed.³ The search for "blockers" was attempted by performing the "blocking test" of Wiener⁴ in the early cases. This was later substituted for the simpler and more sensitive "conglutination" test.⁵

We believe that if either agglutinins or blockers were present they would be detected with the techniques employed.

The bloods from the babies were studied to determine the Rh type, the hemoglobin, and whether there was an increase in the number of normoblasts from the expected normal in order to detect early symptoms of hemolytic disease. They were not allowed to nurse until we were convinced that there was no evidence of iso-immunization in the mother, because it has been shown that Rh antibodies may be found in maternal milk.

Of the 91 Rh-negative women in our series, there is no information on 16 of them (Table II). Seventy-three did not show evidence of iso-immunization, as there were no agglutinins or blockers present in their serum. Their babies were clinically well with hemoglobins over 110 per cent and no increase over the expected number of nucleated red blood cells in the peripheral blood. Only 52 out of these 73 women gave birth to Rh-positive infants, the rest of the siblings were Rh negative.

In the bloods of only two of these Rh-negative mothers bearing Rh-positive children anti-Rh agglutinins were detected. This makes an incidence of one Rh-negative woman out of every 26 becoming sensitized to the Rh factor through pregnancy. This figure is practically the same as found in the United States.

These two cases will be discussed in detail: a third case of an Rh-negative mother who gave birth to a child who died one hour later of erythroblastosis fetalis which was referred to us for blood studies by Dr. Parés will also be discussed.

Among the group of Rh-negative women showing no evidence of isoimmunization to the Rh factor by serological tests, two of them had stillborn babies; the death of one could be attributed to a severe pre-eclamptic toxemia of the mother, and the other one to positive maternal serology. The latter fetus was macerated and had congenital anomalies.

CASE 1.—L. D., a white woman with two living children, gave birth to a healthy baby girl. Mother group O Rh negative, baby group O Rh positive; weak anti-Rh agglutinins (titer 1) present in mother's serum. Baby's hemoglobin when born was 120 per cent; no normoblasts were seen in blood smears; she did not develop jaundice or anemia.

CASE 2.—J. A., a group B Rh-negative woman with four living children, gave birth to a male child group B, Rh positive. The mother's serum contained strong anti-Rh agglutinins (titer 32). The baby developed slight jaundice and anemia (hemoglobin went down to 81 per cent four days after birth) but recovered without transfusion therapy.

CASE 3.—T. G., a white woman with the following obstetric history: married at 18 years of age, had three full-term, apparently normal female children from first husband; two living and well at present, one died at 6 months from meningitis.

At 22 years of age the patient married a second husband. First pregnancy terminated in a spontaneous abortion at four months after a fall. In July, 1944, she delivered a full-term male stillborn child. On May 28, 1945, she gave birth to a premature child in very poor condition which died one hour after birth. The estimated date of confinement for this pregnancy was July 6, 1945. The patient had hydramnios. Fetus was premature, of grayish-blue color; had very poor respirations, moderate edema of the face, extremities, and scrotum. Its abdomen was markedly distended and indurated, the liver apparently filling the whole abdomen. After death partial autopsy revealed an enormous liver, the right lower border reaching almost to the right iliac crest, the left lobe covering completely the spleen which was also enlarged. Blood studies revealed the mother to be group O Rh negative and the baby group O Rh positive; the mother's serum contained strong anti-Rh agglutinins as well as Rh blocking antibodies. The titer of these antibodies was not determined.

Pathologic Report.—*

Macroscopic: The specimen consisted of the spleen, gall bladder and liver of a seven-month stillborn fetus. The spleen weighed 30 Gm. and measured 6 by 4 by 3 cm. The capsule was grayish and presented numerous whitish granulations in the surface; it was of a dark wine color. On section, the organ was chocolate colored. The splenic corpuscles and the trabeculae were visible. The liver weighed 150 Gm. and measured 9.3 by 7 by 5.5 cubic millimeters. The capsule was soft and transparent. On section the parenchyma was firm and pinkish, with a slight greenish color. The cut surfaces were homogenous, and the hepatic lobules were not well outlined. The periportal tissue looked edematous. The central portion of the organ was imperfectly fixed. The *gall bladder* was of normal appearance.

Microscopic: Spleen: the Malpighian corpuscles were not very prominent. The red pulp was congested and presented numerous areas of hemorrhage, sometimes surrounding the lymphoid follicles. The sinuses were full of small hematopoietic foci constituted by red blood cells in all stages of maturation from the erythroblastic to that of basophilic and orthochromatic normoblasts.

*Obtained through the courtesy of Dr. E. Koppish from the School of Tropical Medicine, San Juan, Puerto Rico.

Among these elements were also observed megakaryocytes dispersed along the sinuses, especially in those found below the capsule.

Liver: The portal spaces were thick, edematous, and infiltrated with numerous round cells and eosinophiles. The interstitial tissue of the liver was edematous, and contained multiple hematopoietic foci comparable to those seen in the spleen. These elements were evenly distributed throughout the hepatic tissue. Frequently the cells of Kupffer were swollen and contained phagocytized erythroblasts. Around the biliary ducts of medium and large caliber there was dense infiltration constituted by round cells and polymorphonuclears; the walls of these ducts were thickened by fibroblastic proliferation.

Gall bladder: The mucosa was practically completely autolized. The mucous membrane was thick and edematous, and also the other coats. They were all diffusely infiltrated by small foci of lymphocytes and plasma cells.

Diagnosis: Erythroblastosis fetalis; chronic cholangitis.

Conclusions

This study illustrates some points which are of interest: (1) The low incidence of iso-immunization among Rh-negative women giving birth to Rh-positive children, two out of 54 in our series. (2) The correlation between the presence of Rh antibodies in the mother's serum and the baby's clinical manifestations. Of the babies born of the Rh-negative women who became iso-immunized to the Rh factor, one was not affected at all (Case 1), mother's blood had very weak anti-Rh agglutinins. The baby in Case 2 showed very mild symptoms of icterus gravis which required no treatment. Moderately strong anti-Rh agglutinins were present in the mother's serum. Case 3 gave birth to an infant who died one hour later, showing the clinical and pathologic findings of a severe form of erythroblastosis fetalis; strong anti-Rh agglutinins, as well as blocking antibodies, were found in the mother's blood.

I wish to express my gratitude to Dr. Alexander S. Wiener of Brooklyn, New York, for his valuable criticism of this paper.

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TOTAL HYSTERECTOMY

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A GREAT deal has already been written with reference to the use of total abdominal hysterectomy as a routine procedure in the removal of the uterus for benign disease. The outstanding argument in favor of removal of the cervix at the time of hysterectomy has been that it removes the possibility of subsequent development of carcinoma of the cervical stump. Less important arguments are the removal of the cervix as a possible cause of subsequent leucorrhea or focus of infection. The chief argument against the total hysterectomy as a routine procedure has been that the operative mortality and post-operative morbidity rates are higher with total than with subtotal hysterectomy. The factor of higher mortality with the total hysterectomy is borne out by smaller series of cases in the literature, but not by the large series. On the contrary, the larger series of total hysterectomies, as a general rule, show a lower mortality rate.^{9, 17, 19} With few exceptions, the recommendation has been for more extensive use of the total operation, but many authors qualify this by emphasizing the importance of the skill of the individual surgeon, the consideration of increased risk because of obesity, adhesions, and fixation of the uterus, as well as the patient's general medical condition. While these authors are hesitant to advise routine panhysterectomy for "the occasional operator," they use this procedure routinely themselves and advise it for the skilled operator as a prophylaxis against subsequent cancer changes in the residual cervical stump. Objections to total hysterectomy because of shortening of the vagina or prolapse of the vault are not considered valid, since these complications need not develop if the operation is properly performed.

I. Mortality

In an eleven-year period ending May 31, 1946, 1,798 hysterectomies were performed on the gynecologic service of Bellevue Hospital. Of this number, 1,583 were subtotal hysterectomies and 215 were total hysterectomies. Of these 215, over one-half were performed in the last three years of this eleven-year period, and 165 in the last five years of this period. During the early years of this period, most of the total hysterectomies were for carcinoma of the fundus. In recent years, however, the operation of total hysterectomy for benign cases has become increasingly frequent.

By comparison with other series presented in the literature, these 215 total hysterectomies represent a small series. They were done for both malignant and benign conditions. The operative mortality rate for the group was 2.32 per cent, a total of five deaths, as compared with an operative mortality rate of 1.76 per cent, a total of 28 deaths, for the 1,583 subtotal hysterectomies.

An analysis of these five total hysterectomy deaths reveals the fact that in none of them could death be definitely attributed to the fact that a total hysterectomy was performed rather than a subtotal. The deaths were due to causes that would complicate a subtotal operation with as much frequency as they would a total hysterectomy. Table I summarizes the deaths occurring in the total hysterectomy group.

TABLE I. SUMMARY OF THE FIVE POSTOPERATIVE DEATHS IN THE TOTAL HYSTERECTOMY GROUP

| PATIENT | AGE | MEDICAL COMPLICATIONS | OPERATION PERFORMED BY | OPERATION BESIDES TOTAL HYSTERECTOMY | OPERATIVE FINDINGS | CAUSE OF DEATH |
|---------|-----|-------------------------------------|------------------------|--------------------------------------|-------------------------------|---|
| D. A. | 42 | None | Resident | Bilateral salpingo-oophorectomy | Endometrial polyps cervicitis | Shock paralytic ileus 4th postoperative day |
| B. O. | 42 | Diabetes | Resident | Left salpingo-oophorectomy | Fibroids tubovarian abscess | Pulmonary embolus 7th postoperative day |
| F. R. | 62 | Hypertensive cardiovascular disease | Attending | Bilateral salpingo-oophorectomy | Carcinoma of ovaries | Pulmonary edema 4th postoperative day |
| M. H. | 64 | Hypertension | Attending | Bilateral salpingo-oophorectomy | Post radiation Ca of fundus | Cerebral thrombosis 7th postoperative day |
| E. P. | 40 | None | Resident | Bilateral salpingo-oophorectomy | Bilateral pyosalpinx | Pulmonary embolus 1st postoperative day |

Cardiovascular accidents and pulmonary emboli occur with both types of operation. The percentage of incidence of deaths from pulmonary embolus in total hysterectomy was 0.9 per cent, as against 0.6 per cent for subtotal hysterectomy.

It would seem right to assume with a greater number of total hysterectomies being performed that the operative mortality from total hysterectomy on this service should be reduced. At the present time, however, total hysterectomy on the Bellevue service carries with it a higher mortality rate than does the subtotal.

II. Postoperative Morbidity

A. *Temperature*.—The average temperature reading of 150 total and 150 subtotal hysterectomies selected from roughly the same period of time were compared. Six temperature readings per day for the day of operation and the first seven postoperative days were averaged, but only the 6 A.M. and 6 P.M. temperatures were finally used, since these were the only temperatures taken with regularity in all cases. Statistical analysis revealed no significant difference between the two groups until the 6 P.M. temperature of the third postoperative day. It was found that from this time on through the sixth postoperative day a slight but statistically significant difference existed, the total hysterectomies running a slightly higher temperature for this period of time (Fig. 1). The fact that this slightly higher average temperature exists in the total group relatively late in the postoperative course is probably caused by a low-grade inflammatory reaction about the sutures in the vaginal vault. Although the vagina was surgically prepared pre-operatively in all cases, it is impossible to create a completely sterile field in the vaginal vault.

B. *Catheterization*.—The same 300 patients, 150 total and 150 subtotal, had their charts carefully examined for the necessity of postoperative catheterization. It was found that more patients with subtotal hysterectomies had to be catheterized than those with total hysterectomies. On the day of oper-

ation 28 per cent of the subtotal required catheterization, whereas, 22.3 per cent of the total group required catheterization. On the first postoperative day about an equal percentage of each group required catheterization. More patients in the subtotal group, 30.6 per cent, than in the total group, 27.7 per cent, had to be catheterized at some time in their postoperative course. These data are summarized in Table II.

TABLE II. PERCENTAGE OF PATIENTS REQUIRING POSTOPERATIVE CATHETERIZATION IN 150 TOTAL AND 150 SUBTOTAL HYSTERECTOMIES

| TYPE OF OPERATION | PER CENT REQUIRING CATHETERIZATION AT ANY TIME | DAYS POST OPERATIVE | | | | | | | |
|-------------------|--|---------------------|------|------|-----|-----|-----|-----|-----|
| | | O.R. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| Total | 27.7 | 22.3 | 20.9 | 11.4 | 7.4 | 3.3 | 1.3 | 1.3 | 1.3 |
| Subtotal | 30.6 | 28.0 | 20.0 | 8.7 | 4.7 | 3.3 | 1.3 | 1.3 | 0.6 |

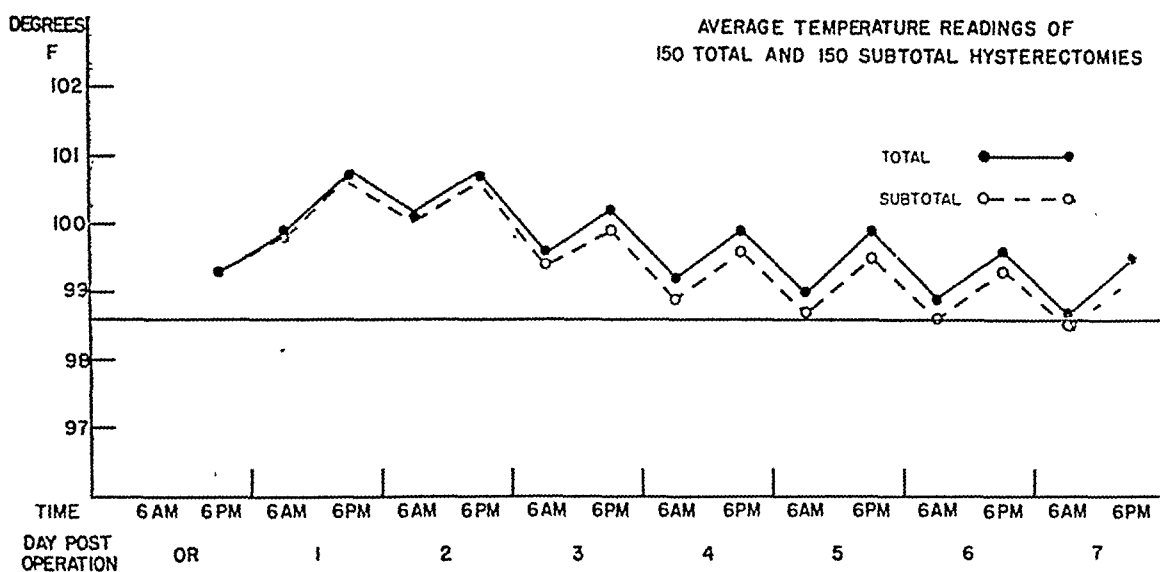


Fig. 1.—Composite temperature charts of 150 total and 150 subtotal hysterectomies.

TABLE III. NUMBER OF POSTOPERATIVE PATIENTS SHOWING SLIGHT, MODERATE, OR MARKED DISTENTION IN 150 TOTAL AND 150 SUBTOTAL HYSTERECTOMIES

| DAY OF OPERATION | | O.R. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|------------------|----------|------|----|----|----|---|---|---|---|
| Total | Slight | 2 | 16 | 23 | 13 | 1 | 1 | 1 | 1 |
| | Moderate | 0 | 6 | 8 | 5 | 4 | 2 | 0 | 0 |
| | Marked | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 |
| | Total | 2 | 22 | 31 | 18 | 6 | 4 | 2 | 2 |
| Subtotal | Slight | 1 | 16 | 24 | 12 | 3 | 0 | 0 | 0 |
| | Moderate | 0 | 2 | 6 | 11 | 0 | 0 | 0 | 0 |
| | Marked | 0 | 0 | 0 | 0 | 2 | 2 | 2 | 2 |
| | Total | 1 | 18 | 30 | 23 | 5 | 2 | 2 | 2 |

C. *Distention*.—This same group of 150 total hysterectomies and 150 subtotal hysterectomies was carefully analyzed as to postoperative distention, and no significant difference found either as to the number of patients who became distended or as to the degree of distention in each group (Table III).

III. The Skill and Experience of the Surgeon

Sixty-five per cent of the total hysterectomies were performed by the resident staff.

Much has been written as to the inadvisability of the total hysterectomy being performed by the occasional operator, and most authors are in agreement that in skilled hands mortality and complications are lower. Goodall⁶ advised the skilled surgeon to become as proficient in the total as in the subtotal. Ward¹⁶ states that in average hands mortality, injuries to bladder and ureters, infection and lack of vaginal support will be higher; for himself he prefers the total operation as a prophylaxis against carcinoma of the cervical stump. Foss and Babcock²⁴ advise against total hysterectomy for the occasional operator. Gaston,²⁶ presenting a personal series, believes the total operation may be safely utilized by the general surgeon of average experience. In general, no one seems to doubt the superiority of the total hysterectomy when, as Martzloff²¹ puts it, the operation is used by well-qualified individuals as an elective procedure without additional hazard to the patient. It would seem the duty, therefore, of any teaching service, turning out supposedly well-qualified gynecologic residents, to make sure its residents have become skilled in this procedure.

IV. Sexual Response Following Hysterectomy

One of the objections voiced but not written against total hysterectomies is that removal of the cervix will interfere with the sexual response of the female. However, Gaston²⁶ mentions that 85 per cent of his total hysterectomy patients experienced no change in their sexual life both in so far as libido and orgasm were concerned.

Sixty-five patients who led a sexual life of any activity whatsoever were carefully questioned as to frequency, desire, satisfaction (orgasm), and dyspareunia. Thirty-four had had subtotal hysterectomies and 31 had had total hysterectomies. They were further divided into those with ovarian tissue remaining and those without ovarian tissue. A general estimation of the effect of the operation on the sexual life of these two groups was then made and classified as improved, unchanged, slightly deteriorated, and deteriorated. As shown from Table IV, there was no significant difference between the subtotal

TABLE IV. SEXUAL SATISFACTION AND DESIRE FOLLOWING HYSTERECTOMY

| | IMPROVED | UNCHANGED | SLIGHT DETERIORATION | DETERIORATION |
|------------------------------|----------|-----------|-------------------------|---------------|
| <i>Total Hysterectomy</i> | | | | |
| Both Ovaries Removed | 5 | 7 | 3 | 4 |
| Ovarian Tissue Remaining | 4 | 3 | 3 | 2 |
| Totals | 9 | 10 | 6 | 6 |
| Percentage | (29.0%) | (32.2%) | (19.4%) | (16.9%) |
| <i>Subtotal Hysterectomy</i> | | | | |
| Both Ovaries Removed | 3 | 8 | 3 | 4 |
| Ovarian Tissue Remaining | 6 | 6 | 2 | 2 |
| Totals | 9 | 14 | 5 | 6 |
| Percentage | (26.5%) | (41.2%) | (14.7%) | (17.6%) |

and total group, 61.2 per cent of the total group being improved or unchanged, as against 68.7 per cent of the subtotal group being improved or unchanged. It did not seem to matter whether or not ovarian tissue remained. The presence or absence of ovarian tissue did not effect the desire of either group except in the small number of patients in each group who claimed marked deterioration of sexual desire and satisfaction following operation. Fifty-three of sixty-five patients, or 81.5 per cent, after hysterectomy and of whom more than one-half no longer had ovarian tissue, claimed improvement, no change,

or only slight decrease in desire or only some delay in achieving orgasm. This should be proof enough that the deterioration in sexual response claimed by the remaining 18.5 per cent was not based on organic changes.

All but three of the patients questioned were under 50 years of age. The three patients over 50 were all total hysterectomy patients. One (aged 53 years) claimed improvement, one claimed no change (aged 52 years) and one claimed marked deterioration (aged 57 years) following total hysterectomy. Except for these three patients, the age distribution was approximately the same in both groups.

One gained three very definite impressions from careful discussion with these 65 patients. The first was that the presence of the cervix has nothing to do with the production of orgasm in the female. The same can be said about the ovary and body of the uterus. Second, a certain number of patients after hysterectomy, regardless of whether they are total or subtotal, will show some deterioration in sexual reaction. Most of these which we have classified as slightly deteriorated were patients who still had orgasm, but experienced some difficulty in reaching this point of satisfaction as quickly as they had prior to operation. Eighteen per cent of the subtotal group and 19 per cent of the total group claimed a marked deterioration. The idea of castration as being something shameful was not voiced by more than two or three of the entire 65 patients, but it was undoubtedly in the minds of many more than this. These two or three admitted it and also admitted the fact that they concealed their inability to conceive from their sexual partner or partners. The presence of the childbearing organs, regardless of whether or not they are diseased or whether or not birth control is practiced, is apparently an important factor in the sexual response of many women, and removal of these organs undoubtedly influences their sexual psyche. Most women after hysterectomy adjust themselves to this however, which brings us to the third impression, the antithesis of the second. Of those women claiming improvement of their sexual satisfaction and increase in libido, several frankly attributed it to the fact that they were no longer fearful of becoming pregnant. Many were women with children in their teens or with large families for whom each sexual act prior to operation apparently raised the subconscious fear of pregnancy, thus diminishing their desire and their satisfaction. Hysterectomy, total or subtotal, with or without remaining ovarian tissue, had rendered the sexual act a thing of pleasure alone to them.

Not only does this study deny the idea that the cervix is a necessary organ to be stimulated in order to achieve orgasm, but it also shows that neither uterus nor ovaries are necessary for its attainment. It only emphasizes the importance of the psychological factor in the female sexual response. The best example was a 45-year-old attractive, Puerto Rican woman in this series, who had two grown children and who was living with a man to whom she was not married, but for whom she cared very deeply. She was discharged from the hospital on her fourteenth postoperative day following total hysterectomy. The next day, fifteen days after total hysterectomy and bilateral salpingo-oophorectomy, she and her partner renewed their active sexual life which involved a frequency of five times a week. When seen six weeks and again three months postoperatively she stated her desire was the same as before operation and her satisfaction even greater because she no longer feared pregnancy.

Finally, then, it must be concluded that where deterioration of the sexual response occurs after hysterectomy with or without oophorectomy, this deterioration is due to the psychic trauma of the castration and not to organic changes or loss of tissue.

V. Postoperative Complications Following Total Hysterectomy

Table V presents all the complications except wound infections following 215 consecutive total hysterectomies. Comparison of the frequency of these complications with the frequency of their occurrence in subtotal hysterectomy was made in only certain of these groups. Urinary tract infection was about

TABLE V. POSTOPERATIVE COMPLICATIONS FOLLOWING TOTAL HYSTERECTOMY
(BASED ON 215 CONSECUTIVE TOTAL HYSTERECTOMIES)

| | | NUMBER | PER CENT |
|-----------------------------------|---|--------|----------|
| Urinary tract infection | | 6 | 2.79 |
| Intestinal obstruction | | 4 | 1.86 |
| a. Requiring ileostomy | 1 | | |
| b. Paralytic ileus | 3 | | |
| Parametritis, cellulitis | | 3 | 1.39 |
| Thrombophlebitis | | 3 | 1.39 |
| Pneumonia | | 4 | 1.86 |
| Cardio-vascular accident | | 4 | 1.86 |
| a. Coronary occlusion | 1 | | |
| b. Cerebral hemorrhage | 1 | | |
| c. Pulmonary edema | 2 | | |
| Hemorrhage from the vaginal vault | | 2 | 0.93 |
| Pulmonary embolus with death | | 2 | 0.93 |
| Lung infarct | | 1 | 0.40 |

the same in both groups. Intestinal obstruction was not compared, since in most instances in both types of hysterectomy this complication seemed dependant upon the presence of adhesions from previous operations or the character of the pelvic lesions rather than on the type of hysterectomy performed. Parametritis and cellulitis, when compared with the incidence occurring in 150 cases of subtotal hysterectomy, were found to be much less frequent in total hysterectomy, where the incidence was 1.39 per cent, as against an incidence of 6 per cent in subtotal hysterectomies. Pneumonia and cardiovascular accidents were not compared. Hemorrhage from the vaginal vault, requiring packing and transfusion, occurred twice. Pulmonary embolus with death occurred twice in these 215 total hysterectomies, an incidence of 0.93 per cent, as compared with an incidence of 0.6 per cent in 1,583 subtotal hysterectomies.

The incidence of *wound infection* was found to be slightly higher in 150 total hysterectomies than in 150 compared subtotal hysterectomies. The percentage incidence was 8.7 for the total group, as compared with 6.6 for the subtotal group.

VI. Follow-Up Complications of Total Hysterectomy

Table VI summarizes the pertinent follow-up findings after total hyster-

TABLE VI. FOLLOW-UP COMPLICATIONS OF 215 TOTAL HYSTERECTOMIES

| | | NUMBER | PER CENT |
|---|---|--------|----------|
| Granulation tissue in vaginal vault | | 33 | 15.30 |
| Leucorrhea | | 9 | 4.13 |
| Slight shortening of the vagina | | 3 | 1.39 |
| Delayed healing of vaginal vault | | 3 | 1.39 |
| Delayed induration about vaginal vault | | 3 | 1.39 |
| Cystocele, rectocele or both | | 3 | 1.39 |
| Vesicovaginal fistula | | 2 | 0.93 |
| a. Carcinoma of cervix with extensive radiation | 1 | | |
| b. Spontaneous healing | 1 | | |
| Kinked ureter (neither re-operated) | | 2 | 0.93 |
| Temporary rectovaginal fistula | | 1 | 0.40 |

ectomy. Granulation tissue in the vaginal vault on the first postoperative visit is very commonly seen, and usually disappears after about six weeks. Specific leucorrhea, usually trichomonas in type, cannot be considered related to the type of operation. Slight shortening of the vagina, one of the frequently voiced objections to the total operation, occurred in only three instances, and it should be emphasized that this shortening in all three instances was only slight. Delayed healing of the vaginal vault and delayed induration about the vaginal vault were temporary findings only. Relaxation of the vaginal walls but not of the vault appeared in three cases; incidentally, McKinnon and Counsellor¹⁹ in a series of patients operated on for vaginal prolapse found only one case of vaginal prolapse following total hysterectomy, whereas 23 cases had a prolapsed cervical stump. One of the two cases of vesicovaginal fistula occurred following extensive radiation for carcinoma of the cervix, and cannot be rightly attributed to the fact that a total hysterectomy had been performed. The other case of vesicovaginal fistula, which also had a kinked ureter and hydronephrosis, was most certainly due to the fact that a total hysterectomy had been performed. This particular operation was performed by a resident, and the technique utilized differed from the usual technique* of the service in that clamps were used along the paracervical tissue and the bloody angles, which possibly caused the kinking of the ureter when too much tissue was incorporated in the suture. This patient was readmitted to the hospital and, while under observation, fortunately had spontaneous healing and cure. The temporary rectovaginal fistula, an accident which occurred once, was the result of an accidental laceration of the rectum at the time of operation; this patient had chronic salpingitis with a tubo-ovarian abscess firmly adherent to the uterus, sigmoid, and rectum; had a subtotal hysterectomy been performed, an abdominal or cervical fecal fistula surely would have developed.

VII. The Argument: Total Versus Subtotal

Table VII shows the incidence of purely benign but rather annoying subsequent symptoms and disease found in 150 cases of supracervical hysterectomy. Six per cent developed a cervicitis that was not present prior to operation. There was profuse and troublesome bleeding from the cervical canal in 2.66 per cent of cases. These follow-up complications are annoying, but certainly not serious. By the same token postoperative hemorrhage from the

TABLE VII. FOLLOW-UP COMPLICATIONS OF 150 SUBTOTAL HYSTERECTOMIES

| | NUMBER | PER CENT |
|---------------------------------------|--------|----------|
| Cervicitis not present preoperatively | 10 | 6.00 |
| Cervicitis present preoperatively | 7 | 4.66 |
| Specific leucorrhea | 5 | 3.30 |
| Profuse bleeding from cervix | 4 | 2.66 |
| Normal menses | 3 | 2.00 |

*The technique generally followed in recent years has been to achieve exposure of the uterine vessels as far down as possible to the cervicovaginal junction by sharp dissection of the adjacent broad ligament, paracervical tissue, and bladder. The vessels are then suture ligated, clamped and cut a little below the level of the internal os and then dissected free from the cervix with scissors. Progressive downward clamping and sharp dissection with the clamps always being applied medial to the vessels and incorporating minimal amounts of tissue follow. Sutures are tied down on the vessel stumps rather than around them after the uppermost suture ligature has been placed. This prevents the incorporation of too much parametrial tissue in the sutures and minimizes the danger of tying off or kinking the ureters. In benign cases when the vaginal vault is incised, the final extirpating incision is carried around the vault in the angle of the fornices, thus preventing shortening of the vagina. The vaginal vault is usually closed tight with interrupted sutures. The stumps of the uterine vessels may be attached to the central or lateral aspects of the closed vault in an attempt to provide the vault with the support of the cardinal ligaments. The round ligaments and tubes are not sutured to the vault, but are inverted in a purse-string suture of the cut edges of the broad ligaments; this continuous suture is continued on as a continuous over and over suture approximating the anterior bladder flap to the peritoneum of the posterior aspect of the vaginal vault.

vaginal vault and slight shortening of the vagina, the latter avoidable if the operation is properly performed, are complications that cannot be considered important. The prevention of subsequent development of cancer of the cervical stump most certainly outweighs these complications. Does it outweigh the higher mortality of the total operation? The possibility of cancer developing in the residual stump is estimated at as high as 2 per cent by McKinnon and Counsellor¹⁹ and at less than 1 per cent by Martzloff. Assuming that 1.5 per cent of our 1,583 subtotal hysterectomies developed cancer of the cervical stump, and assuming a 27 per cent salvage rate (see Behney),¹² this would add 17 preventable deaths to the subtotal group, thus bringing the subtotal mortality to 2.8 per cent. Assuming that 1 per cent of the 1,583 cases developed cancer of the stump, and assuming as high a salvage rate as 40 per cent, this would still make enough preventable deaths to bring the subtotal rate slightly in excess of our total hysterectomy mortality rate. This is certainly not an argument for *routine* panhysterectomy in average hands; however, it should be regarded as an argument for panhysterectomy in benign cases where this operation can be performed without subjecting the patient to additional danger because of difficulty encountered in performing the total hysterectomy. Cancer of the cervix can develop in a nulliparous cervix that at one time was a clean cervix. Conversely, most cervixes with cervicitis, lacerations, and erosions never develop cancer. *Would it not be better, therefore, if the decision to perform a total or a subtotal hysterectomy with a proved benign cervix be dependent more on the factor of ease of operation rather than on whether or not the cervix is clean.* Admittedly, more consideration should be given the total hysterectomy in the presence of cervicitis, but why leave in a clean but useless cervical stump if it is just as easy to remove it?

There should be no need to emphasize the importance of adequate pre-operative examination of the cervix with biopsy of suspicious lesions and ideally of all lesions of the cervix. As a case in point one of the total hysterectomies in this series was done for bilateral parovarian cysts and for what was thought to be chronic cervicitis; pathologic examination of the removed uterus, however, revealed a very early League of Nations Stage I carcinoma of the cervix.

Summary

1. The mortality rate for total hysterectomy is higher than for subtotal hysterectomy in this series of 215 total hysterectomies. However, larger series in the literature, undoubtedly with selection of cases, show a higher mortality for the subtotal procedure. Increased skill from doing more and more total hysterectomies as well as proper selection of cases should reduce the mortality from total hysterectomy. Proper selection of cases involves the *ease with which the operation may be performed*, the skill of the operator, the patient's general condition, the degree of fixation of the uterus, adhesions, obesity, etc. Increased mortality is the only valid objection to the procedure and even this is not a tenable argument when the number of deaths from the possibility of cancer developing in the residual cervical stump are taken into account. *The prevention of cancer of the cervical stump is an adequate reason for performing total hysterectomy in benign cases as long as the operation does not introduce an element of extra danger to the patient.*

2. In so far as postoperative reaction is concerned, patients having had total hysterectomies will run a slightly higher temperature for a longer period

of time. Catheterization is slightly less frequent in total hysterectomies than in subtotals. Postoperative distention is approximately the same in each group.

3. The only postoperative complication that can be considered a valid objection is the possibility of injury to the bladder and/or ureters; proper technique should avoid this complication as well as that of prolapse or shortening of the vaginal vault.

4. Sexual response in women following hysterectomy is not significantly different with the cervical stump remaining than with the cervix removed. Indeed, the cervix, uterus, and ovaries seem to have little to do with libido or sexual satisfaction. Where there are changes in libido or sexual satisfaction following hysterectomy, the cause of these changes is undoubtedly psychogenic.

5. Any teaching service should consider it its duty to turn out gynecologic residents skilled in performing a total hysterectomy.

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A COMPARISON OF THE EFFECTS OF COMMERCIAL AQUEOUS CORPUS LUTEUM SOLUTIONS AND THE PRESERVATIVE, CHLOROBUTANOL, ON UTERINE MOTILITY IN THE RABBIT*

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SINCE the isolation of progesterone in the pure state in 1934,¹⁻³ it has been amply confirmed that this hormone of the corpus luteum is capable of exerting the physiologic effects previously obtained with crude corpus luteum extracts, notably those effects reported by Corner and Allen⁴ and Hisaw and associates.⁵ Progesterone, in addition to its progestational effects on the endometrium, has been shown to inhibit uterine contractions⁶ and to inhibit the response of the uterus to posterior pituitary oxytocic substance. While in the human there appears little doubt that progesterone is able to modify the pattern of uterine motility, the extent to which this hormone can reduce myometrial response to posterior pituitary extracts remains controversial. The recent findings of Henry and Browne⁷ showing a uterine response to pituitrin throughout the entire human menstrual cycle is in striking contrast to the common clinical observation of the noneffectiveness of posterior pituitary extracts, except during the relatively late stages of pregnancy.

The results of other studies, both previous to and following the isolation of progesterone, have suggested that some other corpus luteum factor may be capable of modifying uterine activity. Robson and Illingworth⁸ prepared two corpus luteum extracts, one of which had a marked inhibitory action on uterine contractions and only a weak progestational activity; the other produced marked progestational effects but failed to inhibit the response of the uterus to pituitrin when tested in vitro. Fevold and Hisaw⁹ also obtained two fractions with different activities with respect to effects on the endometrium and the response of the uterus to pituitrin. Hisaw¹⁰ has used the kymographic tracings obtained by Foster to illustrate a difference in effectiveness of a crude corporin preparation as compared with a purified corporin extract. The former induced both a strong progestational reaction and a refractoriness of the uterus to pituitrin. The latter caused a comparable degree of endometrial change, but the uterus remained responsive to pituitrin. These early observations are of more than historical note because they have never been adequately explained, and provoke the suspicion that some heretofore unrecognized corpus luteum factor may affect uterine motility.

More recently there are claims that certain commercial aqueous corpus luteum solutions may affect uterine activity. Macht¹¹ reported that an aqueous corpus luteum solution lessened the response of rabbit uteri to pituitrin, in vitro. Falls and associates,¹² using the intrauterine balloon method of Moir, found that aqueous corpus luteum solutions were effective in inhibiting the oxytocic action of pituitrin on the rabbit as well as the human uterus. Furthermore, the uterine

*This study was aided by a Faculty Research Fund grant administered by Dr. Norman F. Miller, Department of Obstetrics and Gynecology, University of Michigan Medical School.

contractions of parturient women were inhibited following the administration of these solutions. These authors also summarized the results of their experiences in the use of aqueous corpus luteum solutions in the treatment of various complications of pregnancy, particularly habitual and threatened abortion, where, presumably, excessive uterine activity might be an etiologic or undesirable factor. The percentage of threatened and habitual abortion cases carried successfully to viability appeared to be significantly above that for corresponding control groups. These striking results were particularly remarkable in view of the extreme dissimilarity between the aqueous corpus luteum solutions used and the pure steroid hormone, progesterone.

The object of the present investigation was to submit commercial aqueous corpus luteum solutions to experimental tests similar to those which have been used to determine the effects of pure progesterone on uterine motility. The need for such a study is emphasized by the paucity of published data on this subject, in spite of the not infrequent clinical utilization of these preparations.

Procedures and Methods

In vitro and in vivo methods were utilized to determine the ability of commercial aqueous corpus luteum (A. C. L.) solutions to affect the motility of the rabbit uterus.

In the in vitro studies, approximately one-half of a rabbit uterus was suspended in an oxygenated Locke-Ringer's solution maintained at a temperature of 37.5° C. The volume of the bath was 200 c.c.

For the in vivo studies of uterine motility, rabbits with exteriorized cervixes were prepared essentially according to the method described by Reynolds.¹³ The operative procedure was simplified to the extent that the cervixes were exposed by a longitudinal incision of the vaginal sheath rather than by a complete separation of the vagina from the uterine cornua. In most cases bilateral oophorectomy was performed at the same operation. Uterine activity was recorded by an intra-uterine balloon connected with a Brodie bellows through a water and air transmitting system. In later experiments the bellows was replaced by a mercury manometer which was connected with the intrauterine balloon by a continuous water system.

The aqueous corpus luteum preparations were tested for the effect (1) of continuous daily administration on the intact uterus of normal, castrate and estrogen-treated castrate rabbits; (2) of single intravenous injections on the uterine motility of unanesthetized, castrate rabbits receiving adequate estrogen to insure uterine motility; and (3) on excised uterine segments.

Tests were made of the response of the uterus and uterine strips to pituitrin or pitocin subsequent to daily treatment with A.C.L. solutions, following the addition of the solution to the bath and following intravenous injection. In a few instances, the effect of the solutions on tetanic contractions resulting from previous treatment with pitocin was determined.

Comparable studies were made of the response of the uterus, in vitro and in vivo, to varying amounts of chlorobutanol and to an aqueous solution of soluble corpus luteum extract.*

*The author wishes to express his appreciation to Dr. E. A. Sharp of Parke, Davis & Co. for providing adequate amounts of soluble corpus luteum extract. This material made possible a comparison of the effects of the corpus luteum extractives with and without the preservative, chlorobutanol.

†Acknowledgment is made to Parke, Davis & Co. for generous supplies of Aqueous Corpus Luteum Solution, Parke, Davis; to Abbott Laboratories for supplying Aqueous Corpus Luteum Solution, Abbott, and to Hynson, Wescott, and Dunning for ampules of lutein solution.

Three commercial A.C.L. solutions† were used in this study and will be designated in the text as P.D. C.L. solution, Abb. C.L. solution and H.W.D. C.L. solution, respectively. The solutions are of similar nature in that they represent the water soluble extractives of corpus luteum tissue. In this respect they differ markedly from so-called progestin extracts which possess progestogenic activity and which are derived from lipid extracts of corpus luteum tissue. P.D. C.L. and Abb. C.L. solutions contained 0.5 per cent chlorobutanol as preservative, while H.W.D. C.L. solution contained 0.3 per cent cresol and 0.25 per cent chlorobutanol as preservatives. The manufacturers of P.D. C.L. and Abb. C.L. solutions indicate that these preparations possess no progestogenic activity. Information provided by the manufacturers of P.D. C.L. solution indicate that 18 mg. of the soluble corpus luteum extract used in this study were equivalent to the extractive contained in 1 c.c. of P.D. C.L. solution. The chlorobutanol was prepared and used as 0.5 per cent or 0.25 per cent aqueous solutions.

Effect of Daily Administration of A.C.L. Solutions on Uterine Motility

In these tests of the effects on uterine motility of continuous treatment with A.C.L. solutions, three types of rabbits were used. Three rabbits were oöphorectomized animals and received 10 R.U. of alpha estradiol daily throughout the experimental period; one was a normal, estrous rabbit, while another was an oöphorectomized rabbit which had received 60 R.U. of estrogen daily for five days previous to the initiation of treatment with A.C.L. solution. Records of uterine motility were made previous to and following treatment with the solutions. Uterine response to pituitrin was also recorded. The results of these experiments are summarized in Table I.

TABLE I. EFFECT OF DAILY TREATMENT WITH AQUEOUS CORPUS LUTEUM SOLUTION ON UTERINE ACTIVITY.

| RABBIT NO. | TYPE OF ANIMAL | DAILY ESTROGEN (R.U.) | CORPUS LUTEUM SOLUTION USED | | REMARKS ON CONTRACTIONS FOLLOWING TREATMENT | RESPONSE TO PITUITRIN | |
|------------|----------------|-----------------------|-----------------------------|-----------------|---|-----------------------|----------|
| | | | TOTAL AMOUNT (C.C.) | DURATION (DAYS) | | AMOUNT (C.C.) | RESPONSE |
| 4 | Castrate* | None | 12 | 4 | Increased amplitude, frequency unchanged | 0.1 | + |
| 7 | Castrate | 10 | P.D. C.L. | 8 | Reduced frequency | 0.1 | + |
| 8 | Normal | None | Abb. C.L. | 7 | Unchanged | 0.1 | + |
| 9 | Castrate | 10 | H.W.D. C.L. | 10 | Reduced amplitude | 0.02 | + |
| 10 | Castrate | 10 | H.W.D. C.L. | 7 | Greater amplitude | 0.02 | - |
| | | | Abb. C.L. | | | | |

*This animal had received 60 R.U. of alpha estradiol daily for five days previous to treatment with A.C.L. solution.

When the uterine activity at the end of the treatment periods was compared with the records of motility obtained previous to treatment, little change was observed. In three instances the amplitude was modified (Fig. 1), but in no constant direction. In rabbit No. 7 the rate of contractions was reduced slightly, while in No. 8 there was no noticeable change. In all but one instance there was a marked response to pituitrin (Fig. 1). Rabbit No. 10, which had previously shown a good response to 0.02 c.c. of pituitrin, failed to give any response to the same dosage following treatment.

It is of particular interest to compare the effects of daily treatment with A.C.L. solutions with those of daily progesterone treatment. Fig. 2 illustrates

the characteristic effect of progesterone in the rabbit. In this case, after four days' treatment with progesterone, uterine motility was virtually absent, and the uterus was nonresponsive to pituitrin. As reported earlier by Reynolds,¹⁴ a marked reduction in amplitude and frequency of uterine contractions usually occurs within one to two hours following subcutaneous injection of adequate amounts of progesterone in oil solution.

Effect of Single Intravenous Injections of A.C.L. Solutions on Uterine Motility

Ten rabbits prepared with cervical fistulas were used to test the effect of single intravenous injections upon uterine motility. After insertion of the balloon a control record of uterine activity was taken for fifteen to twenty

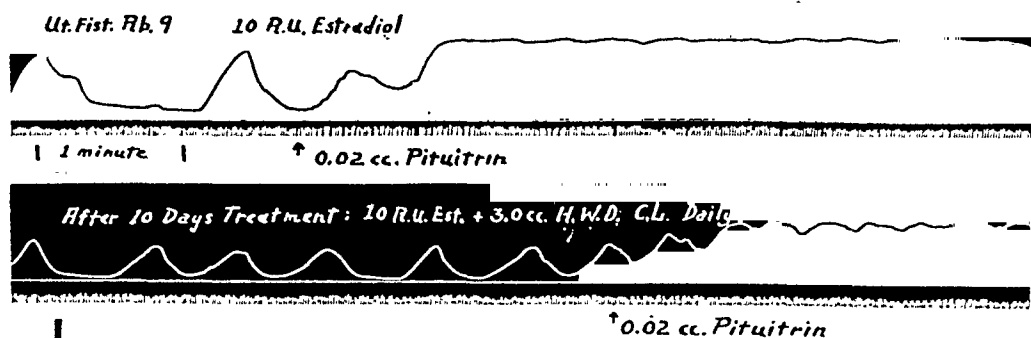


Fig. 1.—Kymographic tracings of uterine motility and response to pituitrin before treatment (upper tracing) and after ten days' treatment with a total of 30 c.c. of H.W.D. C.L. solution. The motility patterns differ but the response to pituitrin is approximately the same. The donor had received 10 R.U. of alpha estradiol daily during the experiment.

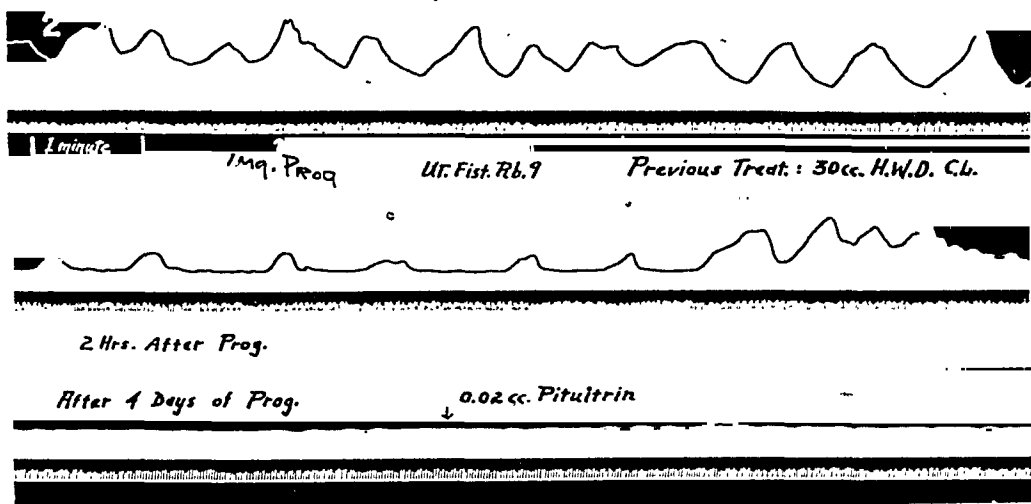


Fig. 2.—Tracings of uterine motility following progesterone treatment. This rabbit (No. 9) had previously been used to test the effectiveness of daily treatment with A.C.L. solution (see Fig. 1). Injection of 1 mg. of progesterone in oil, subcutaneously, resulted in a marked reduction in amplitude and frequency of the contractions (middle tracing). Administration of 0.25 mg. of progesterone daily for three successive days resulted in loss of contractility and refractoriness to pituitrin.

minutes. Usually a fairly regular pattern of motility was established within this period of time characterized by uniformity of successive contractions with respect to amplitude, frequency, and tonus. With two exceptions, all animals had been oöphorectomized at the time the fistula was prepared, and received daily estrogen treatment to insure uterine motility. In most instances the

TABLE II. EFFECT OF SINGLE INTRAVENOUS INJECTIONS OF AQUEOUS CORPUS LUTEUM SOLUTION ON UTERINE ACTIVITY

| RABBIT NO. | DATE OF TEST | DAILY ESTROGEN (R.U.) | A. C. L. SOLUTION USED | | EFFECT ON CONTRACTIONS |
|------------|--------------|-----------------------|------------------------|-------------|--|
| | | | SOLUTION | AMOUNT C.C. | |
| 2 N* | 4/19 | — | P.D. C.L. | 2 | Increased regularity only |
| | 4/23 | — | P.D. C.L. | 4 | Reduced amplitude and frequency |
| 4 C† | 5/21 | 60 | P.D. C.L. | 4 | Progressive reduction in amplitude and frequency to inactivity |
| 5 C | 8/3 | 60 | P.D. C.L. | 4 | Reduced frequency |
| | 8/5 | 60 | P.D. C.L. | 3 | None |
| | 8/26 | 60 | P.D. C.L. | 3 | Reduced amplitude |
| | 9/17 | 60 | P.D. C.L. | 3 | None |
| 6 C | 8/14 | 5 | H.W.D. C.L. | 3 | Marked reduction in tonus |
| | 8/17 | 5 | H.W.D. C.L. | 3 | Reduced tonus |
| | 8/20 | 5 | H.W.D. C.L. | 3 | Reduced tonus |
| 7 C | 9/7 | 10 | H.W.D. C.L. | 3 | Reduced amplitude |
| | 9/9 | 10 | H.W.D. C.L. | 3 | Reduced tonus |
| | 9/10 | 10 | H.W.D. C.L. | 3 | Reduced tonus and frequency |
| | 9/13 | 10 | H.W.D. C.L. | 3 | Reduced frequency |
| | 9/14 | 10 | H.W.D. C.L. | 3 | Reduced tonus and frequency |
| | 9/17 | 10 | H.W.D. C.L. | 3 | None |
| 8 N | 8/31 | — | H.W.D. C.L. | 3 | Marked reduction in tonus |
| 9 C | 9/17 | 10 | H.W.D. C.L. | 3 | None |
| | 9/30 | 10 | H.W.D. C.L. | 3 | Reduced tonus |
| 10 C | 10/5 | 10 | Abb. C.L. | 3 | Marked reduction in tonus and amplitude |
| | 10/6 | 10 | Abb. C.L. | 3 | Slight loss of tonus, reduced amplitude |
| 11 C | 10/12 | 5 | Abb. C.L. | 3 | Gradual reduction in tonus |
| | 10/14 | 5 | Abb. C.L. | 3 | Progressive reduction in tonus, amplitude and frequency |
| 14 C | 7/31 | 10 | Abb. C.L. | 3 | None |

*N indicates a normal estrous rabbit.

†C indicates a bilaterally oophorectomized rabbit.

single injection consisted of 3 c.c. of A.C.L. solution. The amounts of the different solutions used, the amount of estrogen administered daily, and the effect on contractions are tabulated in Table II.

There was considerable variation, both qualitatively and quantitatively, in the effect of the injections upon the established motility pattern. This variation obtained for different animals as well as for different tests on the same animal. In every instance where an effect was noted (78.2 per cent of the tests), the change was toward a less active uterine motility. This change was characterized in some instances by a marked reduction in tonus as well as decreased amplitude and rate of contraction (Fig. 3). In other instances only regularity, frequency, or amplitude was affected. In five tests there was no observable effect upon contractions. The absence of effect is interesting, since in three animals (Nos. 5, 7, and 9) striking effects were obtained in other trials.

A few similar tests were made using either chlorobutanol or soluble corpus luteum extract. The tests with chlorobutanol consisted of injections of 3 c.c. of a 0.5 per cent solution. The soluble corpus luteum extract was dissolved in distilled water in concentrations of 18 mg. to 1 c.c. Three to six c.c. of this solution were used for the several tests.

The motility was reduced or tonus lowered in four of eight trials with chlorobutanol. In four tests with soluble corpus luteum extract there was no effect on uterine motility.

Effect of Soluble Corpus Luteum Extract on Response of Uterus to Pituitrin

Using three rabbits, comparisons were made between the response of the uterus to 0.5 U. of pituitrin and to 0.5 U. of pituitrin plus 108 mg. of soluble

corpus luteum extract (equivalent to the amount of this extract in six 1 c.c. ampules of P.D. C.L. solution). The intervals between administration of pituitrin and the extract were 1.0, 1.5, 4.0, and 4.5 minutes in four tests.

Fig. 4 illustrates the failure of this amount of extract to modify the characteristic recovery from the effects of the oxytocic agent.

Effect of A.C.L. Solutions on Uterine Strips

Table III summarizes the effects of commercial A.C.L. solutions, Soluble Luteum extract, and chlorobutanol on the contractility of uterine strips. Reduced motility or lowered tonus followed the addition of both A.C.L. solutions and chlorobutanol in a majority of instances.

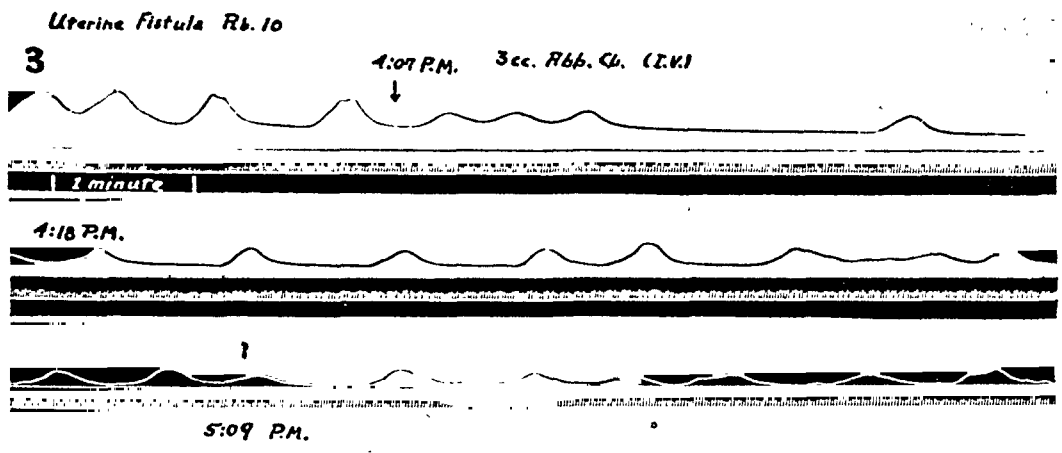


Fig. 3.—Effect of a single intravenous injection of 3 c.c. of Abb. C.L. solution. A decrease in tonus, amplitude and rate of contractions rapidly followed this treatment.

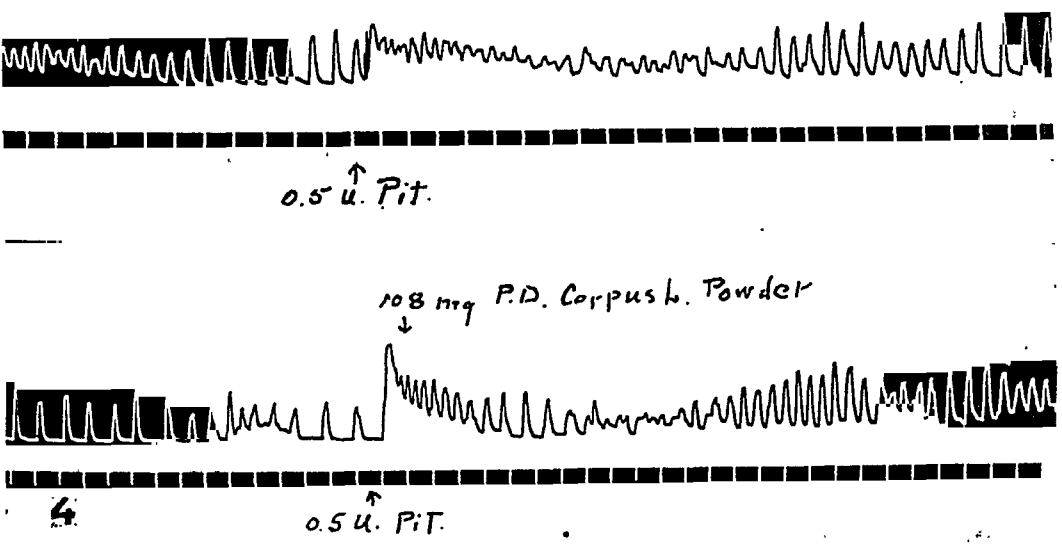
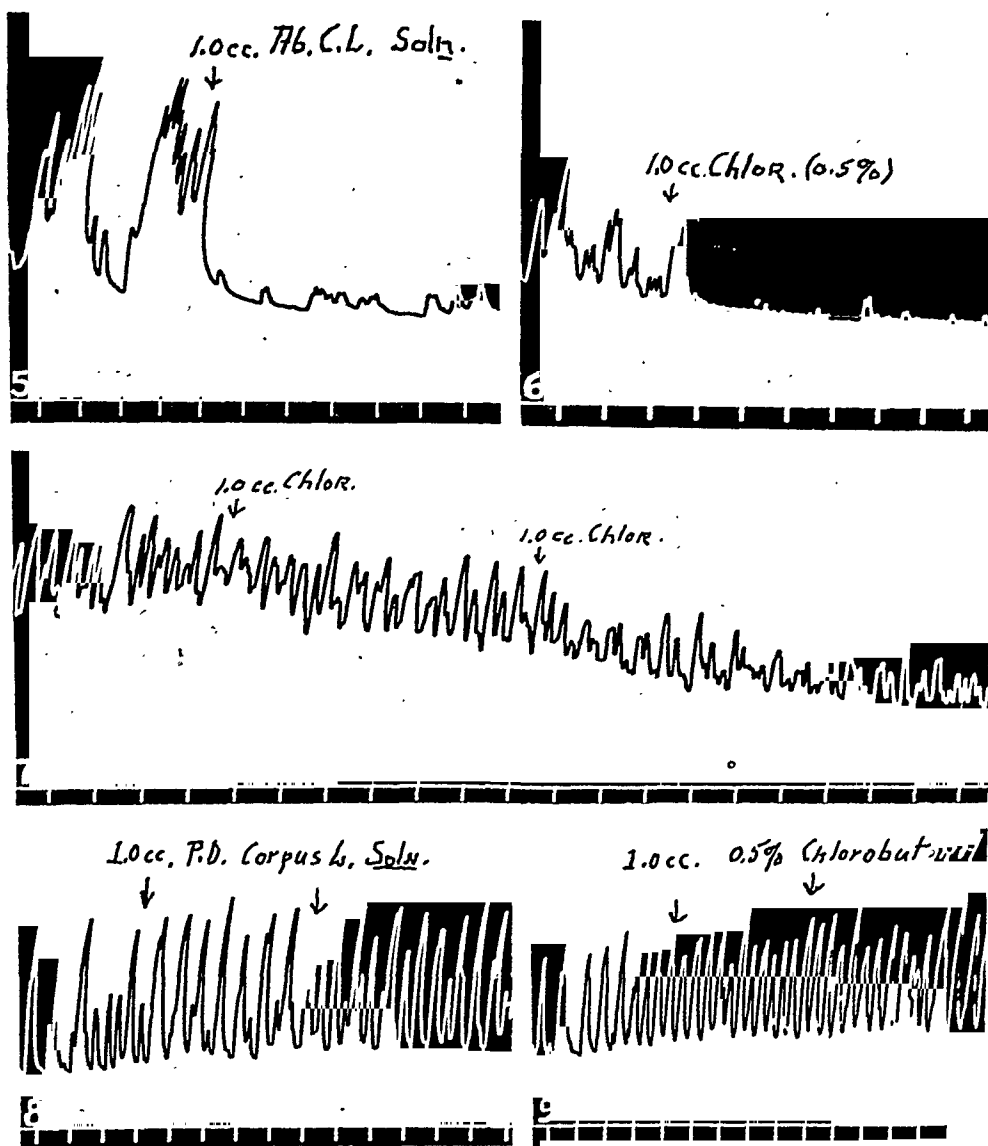


Fig. 4.—Tracings comparing the recovery from the oxytocic effects of Pituitrin (upper tracing) and pituitrin followed by 108 mg. of soluble corpus luteum extract (equivalent to the corpus luteum extractives in 6 c.c. of P.D. C.L. solution). The recovery patterns are very similar. Time in minutes is recorded on the base line.

The addition of 1 c.c. of A.C.L. solution modified uterine motility in 78.9 per cent of the trials while the addition of the same amount of 0.5 per cent chlorobutanol had comparable effects in 86.4 per cent of the tests. Both solutions

were effective in reducing the activity of uteri from castrated and estrogen-treated donors as well as uteri from donors which had been pseudopregnant from two to five days.

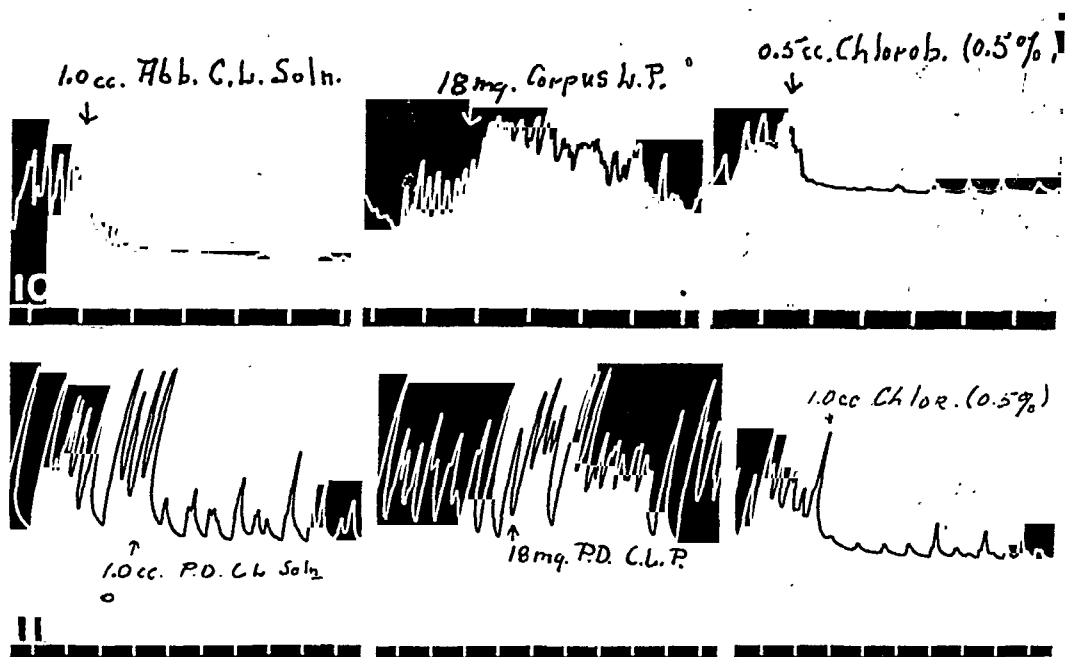
The degree of response to these preparations varied considerably. The most striking and characteristic effect was a reduction in amplitude and frequency of the contractions (Figs. 5 and 6). In numerous tests activity virtually ceased. Frequently reduced activity was associated with a reduction in tonus. In some instances a relative refractoriness to the solutions was exhibited (Fig. 7). In such cases more marked inhibition was attained by increasing the concentration of the solution. Occasionally the uterine strip appeared virtually unaffected (Figs. 8 and 9). It is notable that strips showing relative or complete refractoriness to an A.C.L. solution invariably exhibited a comparable refractoriness



Figs. 5-9.—Kymographic tracings showing several grades of response of uterine strips to A.C.L. solutions and chlorobutanol. Figs. 5 and 6.—Maximal inhibition of contractility following Ab. C.L. solution and chlorobutanol demonstrated on the same uterine strip. The bath was changed between recordings. Fig. 7.—Intermediate grade response to chlorobutanol. Note the progressive decrease in tonus and amplitude with increasing concentration of chlorobutanol. Figs. 8 and 9.—Two tracings obtained from the same uterine strip showing a total refractoriness to both P.D. C.L. solution and chlorobutanol. Bath changed between recordings. Time in minutes is recorded on the base line.

to chlorobutanol. Regardless of the degree of reduced activity, the uterine muscle responded to pitocin or pituitrin.

Soluble corpus luteum extract administered as an aqueous solution failed in every instance to reduce activity. On the other hand, the addition of this extract invariably resulted in increased tonus or activity. Figs. 10 and 11 illustrate the responses of two uterine strips to the three different preparations.



Figs. 10 and 11.—Tracings obtained from two uterine strips comparing the effectiveness of A.C.L. solutions, soluble corpus luteum extract, and chlorobutanol in reducing contractile activity. Fig. 10.—Sections of three tracings on the same uterine strip. The bath was changed between recordings. Abb. C.L. solution and chlorobutanol reduced motility whereas 18 mg. soluble corpus luteum extract (indicated as Corpus L.P. in figure) had a pronounced stimulatory effect. Fig. 11.—Sections from three tracings on another uterine strip. P.D. C.L. solution and chlorobutanol reduced activity while 18 mg. of soluble corpus luteum extract (indicated as P.D. C.L.P. in figure) temporarily increased tonus. Time recorded in minutes on base line.

Discussion

The germicidal and antiseptic properties of chlorobutanol (chlorethane) have resulted in its common use as an effective preservative of numerous pharmaceutical preparations. In some of these preparations, such as extracts of the posterior pituitary, the active hormonal agent has a high degree of pharmacological potency and is effective in relatively small quantities. In such cases it is doubtful that a small amount of preservative agent would either interfere seriously with the action of the active agent or exert any significant effect of its own. On the other hand, when a preparation such as an aqueous corpus luteum solution is administered at frequent intervals, over long periods of time with individual doses of the order of one to three c.c., it would appear important to give consideration to all the physiological and pharmacological properties of that preparation. Since aqueous corpus luteum solutions may consist of extractives dissolved in 0.25 per cent to 0.5 per cent solutions of chlorobutanol, attention must be directed to the possible effects of this solvent.

TABLE III. COMPARATIVE EFFECTIVENESS OF AQUEOUS CORPUS LUTEUM SOLUTIONS, SOLUBLE CORPUS LUTEUM EXTRACT AND CHLOROBUTANOL IN REDUCING THE CONTRACTILE ACTIVITY OF UTERINE STRIPS

| MATERIAL TESTED | TYPE OF DONOR | AMOUNT OF SOLUTION OR EXTRACT (C.C.) | CONCENTRATION OF CHLOROBUTANOL (%) | NUMBER OF TESTS | NUMBER SHOWING REDUCED MOTILITY | PERCENTAGE OF TESTS SHOWING REDUCED MOTILITY (PER CENT) |
|--|---------------------|--------------------------------------|------------------------------------|-----------------|---------------------------------|---|
| Aqueous corpus luteum solutions (0.5 per cent chlorobutanol as preservative) | Estrous | 1.00+ | 0.00125 | 1 | 1 | 78.9 |
| | Estrous | 1.00 | 0.00250 | 19† | 15 | |
| | Estrous | 2.0 | 0.00500 | 5 | 2 | |
| | Estrous | 3.00 | 0.00750 | 1 | 1 | |
| | Castrates receiving | 1.00 | 0.00250 | 5 | 5 | |
| | | 2.00 | 0.00500 | 3 | 3 | |
| | estrogen | 3.00 | 0.00750 | 1 | 1 | |
| | Pseudo-pregnant | 1.00 | 0.00250 | 1 | 1 | |
| | | (MG.) | | | | |
| | Estrous | 18.00 | | 13 | 0 | |
| Soluble corpus luteum extract (no chlorobutanol)* | | 36.00 | | 3 | 0 | 00.0 |
| | Pseudo-pregnant | 18.00 | | 3 | 0 | |
| | | (C.C.) | | | | |
| Chlorobutanol, 0.5 per cent | Estrous | 0.50 | 0.00125 | 4 | 4 | 86.4 |
| | | 1.00 | 0.00250 | 22 | 19 | |
| | Castrates receiving | 2.00 | 0.00500 | 4‡ | 1 | |
| | | 1.00 | 0.00250 | 2 | 0 | |
| | Pseudo-pregnant | 0.25 | 0.00060 | 3 | 0 | |
| | | 0.50 | 0.00125 | 5 | 5 | |
| | | 1.00 | 0.00250 | 2 | 2 | |
| | | | | | | |

*18 mg. of this extract was equivalent to the amount of extractive in 1 c.c. of P.D. C.I. solution.

†The aqueous corpus luteum solution used in this test contained 0.25 per cent chlorobutanol.

‡In two trials a solution containing 0.25 per cent chlorobutanol was used.

§The uterine strips had previously failed to respond to lower concentrations.

The hypnotic and anaesthetic properties of chlorobutanol have long been recognized,¹⁵ and its antispasmodic effect has been utilized in attempts to prevent or relieve nausea.¹⁶ Perhaps in recognition of its antispasmodic effect, chloretone has been used with reported success in the treatment of dysmenorrhea.¹⁷ To the author's knowledge, the only experimental study of the effect of chloretone on smooth muscle contractility is that of Terasaka.¹⁸ This author states that chloretone in concentrations of 0.02 per cent lowered the tonus, in vitro, of excised strips of the small intestine of rabbits, and reduced the spontaneous activity of uterine strips. The report is a brief summary of observations and includes no data. The results of the present investigation not only confirm the findings of the earlier author, but indicate the effectiveness of concentrations of the order of 0.00125 to 0.0025 per cent.

While the effects of aqueous corpus luteum solutions compare very closely with those of chlorobutanol, soluble corpus luteum extract (a water soluble extract of corpus luteum tissue free of any preservative agent) either produced no change in uterine contractility or increased activity. The evidence points

strongly to the probability that the effect of the aqueous corpus luteum solutions was produced by the preservative, chlorobutanol, rather than by a specific factor of the corpus luteum extract.

The A.C.L. solutions used in this study do not possess three physiologic activities which are well established as properties of progesterone: (1) they do not induce progestational changes in the rabbit endometrium (unpublished observations of the author); (2) repeated injections do not result in uterine quiescence; (3) repeated injections do not inhibit the response of the uterus, either in vitro or in vivo, to posterior pituitary extracts.

Falls and co-workers¹² report that treatment of a postpartum subject with 10 c.c. of an aqueous corpus luteum solution, following a previous injection of pituitrin, lowers uterine tonus and slows the rate of the contractions. This type of test was not utilized to any great extent in the present investigation due to the observation that while the recovery following response to pituitrin may in general follow a typical pattern, there may be marked variations with respect both to speed of recovery and amplitude and frequency of contractions. In one experiment described above it was found that an amount of soluble corpus luteum extract equivalent to the extractive contained in 6 c.c. of one of the A.C.L. solutions did not significantly modify recovery from the tetanic contractions induced by pituitrin. In the author's judgment, this type of test cannot be applied satisfactorily to true progestogenic preparations. The progestogenic agent, dissolved in an oil medium, is administered parenterally and a latent period occurs before effective amounts of the hormone can be absorbed. During this interval some degree of recovery from the oxytocic stimulus might be expected which would be unrelated to the injected progestogenic substance.

Macht¹¹ concluded that a uterine strip from a rabbit pretreated with an aqueous corpus luteum solution is less sensitive to pituitrin than a strip from the same animal before such treatment. The present experiments do not disclose whether or not the degree of sensitivity to this drug is altered. They do, however, emphasize that uteri of rabbits treated with these solutions do continue to respond to the oxytocic factor of the posterior pituitary.

The above described results indicate a striking inhibitory effect of chlorobutanol on uterine contractions and emphasize the possibility of this factor exerting a pharmacological effect when these solutions are used clinically or experimentally.

The variations in responsiveness to chlorobutanol have not been explained. In general, the greater the initial spontaneous contractile activity of a uterine strip, the less it was affected by chlorobutanol (compare Figs. 5 and 9). This suggests that some unrecognized physiologic condition of the donor modifies the response of the uterine muscle to the pharmacological agent. The comparative studies on uteri from estrous and pseudopregnant rabbits did not contribute to an elucidation of this problem since uteri from the latter type of animals showed the same variability in responsiveness.

Summary and Conclusions

1. In vitro and in vivo methods were used to test the effect of three commercial aqueous corpus luteum (A.C.L.) solutions, a soluble corpus luteum extract, and the preservative agent, chlorobutanol, on uterine motility in the rabbit.

2. Daily treatment with commercial A.C.L. solutions for four to ten days had no significant effect upon uterine motility, in vivo. A characteristic uterine response to pituitrin was obtained in all but one instance.

3. Single intravenous injections of commercial A.C.L. solutions had varying degrees of effect on uterine motility. In approximately three-fourths of the tests, the effect was in the direction of reduced motility. The effect of chlorobutanol was equally variable but in the same direction. Aqueous solutions of a soluble corpus luteum extract were without effect.

4. In a majority of instances commercial A.C.L. solutions and chlorobutanol reduced the motility of uterine strips. The addition of these preparations to the bath did not interfere with the response of the muscle to oxytocic agents.

5. These studies clearly indicate that the three commercial aqueous corpus luteum solutions tested possess a property capable, under the conditions of the aforescribed experiments, of reducing uterine activity. These preparations contained, as a preservative agent, 0.25 or 0.5 per cent chlorobutanol. It was demonstrated that chlorobutanol itself is capable of reducing the motility of uterine muscle. On the other hand, an aqueous solution of a soluble corpus luteum extract, claimed to be a component of one of the commercial solutions, did not reduce uterine activity. In view of these findings the possibility is suggested that some reports of the effectiveness of commercial aqueous corpus luteum solutions in reducing uterine activity may be due to the chlorobutanol factor rather than to some heretofore unrecognized property of the corpus luteum.

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EPISIOTOMY BLOOD LOSS

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MANY methods are described for measuring blood loss in obstetric patients. But, basically, these are four: Williams¹ measured blood caught in basins. Schmid² weighed bloodstained linen before and after washing and drying, the difference representing grams of blood lost. Pastore³ expressed blood loss as percentage body weight computed from changes in the cell volume during the puerperium. Dieckmann and Daily,⁴ using a modification of Gatch and Little's method,⁵ converted blood and linen washings to acid hematin with 0.1 N hydrochloric acid, and calculated blood loss by formula. Inaccuracies from amniotic fluid, particularly the "after waters," makes the first two methods of less certain value. Coller and associates⁶ and Dieckmann and Daily doubt if a sound correlation exists among changes in hematocrit, hemoglobin, and plasma proteins before and after blood loss. The fourth method, then, is apparently the best.

Few reports exist concerning episiotomy blood loss. Conn and co-workers,⁷ using a modification of Williams' method,¹ reported average total blood loss for primiparas with episiotomy as 397 ml. and 189 ml. without, the calculated difference being 208 ml. Dieckmann and Daily⁴ employed the acid hematin method on fifteen patients and found an average total blood loss (episiotomy plus uterine) of 342.3 ml. These same investigators noted a considerable variation in amounts of blood lost, and reasoned that a larger series would become of little additional value.

Obviously, several factors influence episiotomy blood loss, such as: the type, depth, and duration of anesthesia, parity, extent of episiotomy, traumatic delivery, presence or absence of vulvar varicosities, individual variations, and, of considerable importance, the elapsed time. It has occurred to us that most of these might be controlled in carefully selected cases; that episiotomy blood loss would relate directly to time, and therefore might be expressed as milliliters of blood lost per minute.

Material

A total of 71 patients were selected for study. One group consisted entirely of women with normal pregnancies and uncomplicated labors. In this group pelvic measurements, particularly of the outlet, were adequate. All were primigravidas and the occiput was in an anterior position, two to three centimeters below the ischial spines (low forceps) or crowning at the vulva (outlet forceps), when each experiment was performed. In a second group of patients, also consisting of primigravidas, some complicated deliveries occurred.

Method

Each collection of blood was made with the patient in a lithotomy position, with a double thickness of waxed paper beneath the hips, and with the end of this paper directed toward a floor basin containing about 1,000 ml. 0.1 N hydrochloric acid. Episiotomies, performed with scissors, were all left medio-lateral in location. The operation consisted of three incisions, as described by DeLee⁸: an initial perineal incision, a second cutting intercolumnar fascia and thus exposing levators, and a third incising the vaginal mucosa. Delivery was completed with forceps following the episiotomy incisions.

Three phases of episiotomy bleeding were recognized: that phase from the initial incision until the infant's head distended the vulva and controlled bleeding; phase two, consisting of that time during which the infant is delivered; and phase three, that period after delivery until completion of the episiotomy repair. Significant bleeding occurs only during the first and third phases, and blood was collected separately for these periods. Furthermore, the elapsed times for phases one, two, and three were measured, and blood loss per minute calculated for periods one and three. Oxytocies, consisting of solution of intravenous pituitary or ergotrate or both, were administered during phase two to insure rapid placental detachment. And, following an early expression of the placenta, a tail-sponge was packed against the cervix to contain any additional uterine blood.

Three groups of patients were studied during phase one: those in which no tamponade was employed; another group in which a sponge was stuffed^{*} into the wound; and a third in which bleeding vessels were ligated prior to completion of the delivery by forceps. Ethylene-ether anesthesia was used for each group. Cases investigated under cyclopropane, ether, and spinal anesthesia are reported collectively under total episiotomy blood loss. Except for a few designated cases, the infant was delivered slowly following birth of the head, a method advocated by Dieckmann.⁹

The method for acid hematin extraction was as described by Dieckmann and Daily,⁴ with the exception that the Coleman spectrophotometer Model 11 was used instead of the Duboseq instrument. Blood loss was calculated by the following formula: ml blood loss =
$$\frac{\text{total grams hemoglobin recovered}}{\text{grams hemoglobin/100 ml. patients blood}} \times 100.$$

The recovery ratio for the acid hematin method was tested as follows: Known amounts of blood were poured over four Mayo-type sponges; 1,000 ml. 0.1 N hydrochloric acid was added; the sponges were washed and wrung out by hand in that solution. In a second group the sponges were rinsed in addition in 500 ml. 0.1 N hydrochloric acid; and that solution was added to the original. In both groups the solutions were diluted to the nearest convenient mark for analysis.

Results

Table I lists the recovery ratios by the acid hematin method. In a single washing 83 to 92 per cent was recovered. But, if soiled sponges were rinsed, a consistently higher average of recovery occurred (95 to 98 per cent).

Fig. 1 illustrates total episiotomy blood loss for forty patients. Although the average loss for this group was 253 ml., the variation was considerable. These cases were drawn from the private and clinic services, and episiotomies were left mediolateral in location.

Table II lists total blood loss for the first phase by the previously defined methods. Although the average blood loss per minute was significantly reduced for those with tied vessels and stuffed sponge, *the total blood loss of this*

*Insertion of a folded Mayo-type sponge into the episiotomy wound.

TABLE I. PERCENTAGE RECOVERY OF KNOWN AMOUNTS OF BLOOD BY ACID HEMATIN METHOD

| SINGLE WASHING | | | RINSED SPONGES* | | |
|----------------|------------------|------------------------|-----------------|------------------|------------------------|
| ML. BLOOD | ML. RECOVERED | PERCENTAGE RECOVERY | ML. BLOOD | ML. RECOVERED | PERCENTAGE RECOVERY |
| 25 | 23.0 | 92.0 | 25 | 24.3 | 98.0 |
| 50 | 41.5 | 83.0 | 50 | 48.6 | 97.4 |
| 100 | 91.8 | 91.8 | 100 | 95.4 | 95.4 |
| 250 | 227.5 | 91.0 | 250 | 240.0 | 96.0 |

*Note that a higher percentage of recovery occurred if soiled sponges were rinsed, and this rinse water added to the original solution.

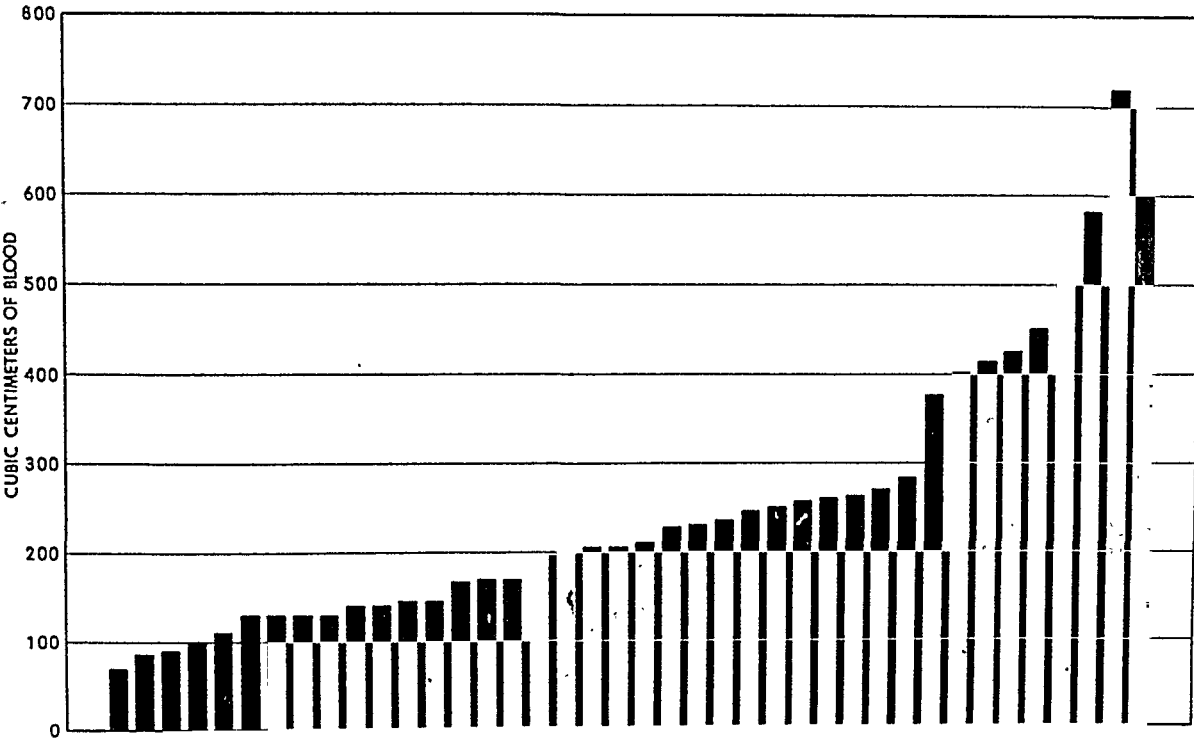


Fig. 1.—Total episiotomy blood loss in forty primigravidas.

TABLE II. BLOOD LOSS DURING FIRST PHASE

| | OBSERVA- TIONS | VARIATION | | AVERAGE ML./MIN. |
|---------------------------------|-------------------|-------------|--------------------|---------------------|
| | | ML. BLOOD | TIME MIN. SEC. | |
| Low forceps, no tamponade | 20 | 46.5 to 289 | 1 10 to 5 45 | 50.1 |
| Stuffed sponge | 8 | 30.1 to 322 | 1 to 4 30 | 56.7 |
| Stuffed sponge and tied vessels | 6 | 94.0 to 339 | 3 to 10 35 | 33.5 |
| Thrombin with sponge | 10 | 72.0 to 322 | 2 40 to 6 42 | 29.6 |
| Outlet forceps, no tamponade | 9 | 28.0 to 74 | 2 to 5 15 | 16.1 |

group was high. The average blood loss for outlet forceps was comparatively low, 16.1 ml. per minute; and the use of thrombin (applied with a Mayo sponge) significantly reduced bleeding. Fig. 2 illustrates graphically the linear relationship between blood loss and elapsed time during phase one.

The average time for twenty primigravidas terminated by slow delivery was three and one-fourth minutes. Seven additional patients were delivered in an average time of one and one-half minutes.

Phase three is listed for slow delivery as well as for more rapid delivery (Table III). Note the marked decrease in the total blood lost and ml. loss per minute for this period as contrasted with that measured during phase one (Table II). In addition, the average loss following slow delivery, 3.1 ml. per minute, was significantly lower than the average (4.4 ml. per minute) following the faster delivery.

TABLE III. BLOOD LOSS DURING THIRD PHASE

| | OBSERVA- TIONS | VARIATION | | AVERAGE ML./MIN. |
|----------------------------|-------------------|--------------|--------------|---------------------|
| | | ML. BLOOD | TIME MIN. | |
| Low forceps, slow delivery | 20 | 43.6 to 190 | 16 to 52 | 3.1 |
| Faster delivery | 7 | 52.5 to 110 | 13 to 30 | 4.4 |

Comment

The efficacy for recovery of hemoglobin by the acid hematin method is consistent. Dieckmann and Daily⁴ recovered 87 to 90 per cent of hemoglobin from known quantities of blood with a single washing. And, if soiled sponges were rinsed, and this rinse water added to the original solution, the recovery was 98 per cent. The results in this report (Table I) confirm their observation.

The results of this study indicate that total episiotomy blood loss may be considerable, and probably constitutes the chief source for blood loss in most primiparous patients. The average total episiotomy loss of 253 ml. is certainly high by comparison, since the uterine blood loss following intravenous ergotrate is reported as less than 100 ml. in 81 per cent of patients,¹⁰ and as low as 51.9 ml. following slow delivery and intravenous pituitrin and ergotrate.⁹

Stuffing a Mayo sponge into the episiotomy wound during phase one does not significantly reduce the total blood loss or decrease that lost per minute. This practice only serves as a wick to soak up the blood, and probably deludes the operator into believing that less blood is lost. Some clinicians clamp and ligate bleeding vessels. But this procedure occupies valuable time, and the total amount lost is increased even though the loss per minute is less. Since the blood lost relates directly to time consumed (Fig. 2), the amount of bleeding can be significantly reduced by shortening phase one. Episiotomy blood loss during this period can be as low as 46.5 ml. (Fig. 2).

A dramatic change occurs in the rate of episiotomy bleeding following delivery (Table III). The marked reduction in ml. lost per minute (50.1 ml. before delivery and 3.1 ml. after delivery in those without tamponade) has two probable explanations. The first concerns the effect of the infant's head and body, which acts as a tamponade during its passage through the introitus, and during which the ends of cut vessels are obliterated by pressure. The lower loss during outlet forceps supports this concept, as does the noticeably greater rate per minute following a faster delivery, when tamponade occurs for a shorter length of time. A second possibility concerns changes in venous circulation before and after delivery. Considerable venous congestion, as evidenced by protruding external hemorrhoids, promotes more bleeding prior to

delivery. Whereas immediately after delivery circulation becomes reestablished between perineal venous plexuses and pelvic veins, and this congestion becomes relieved. Thus, much less episiotomy bleeding occurs during phase three.

Thrombin, applied to the episiotomy with a Mayo-type sponge, was used on ten patients. Blood loss during phase one was reduced and bleeding from that wound after delivery was lessened.

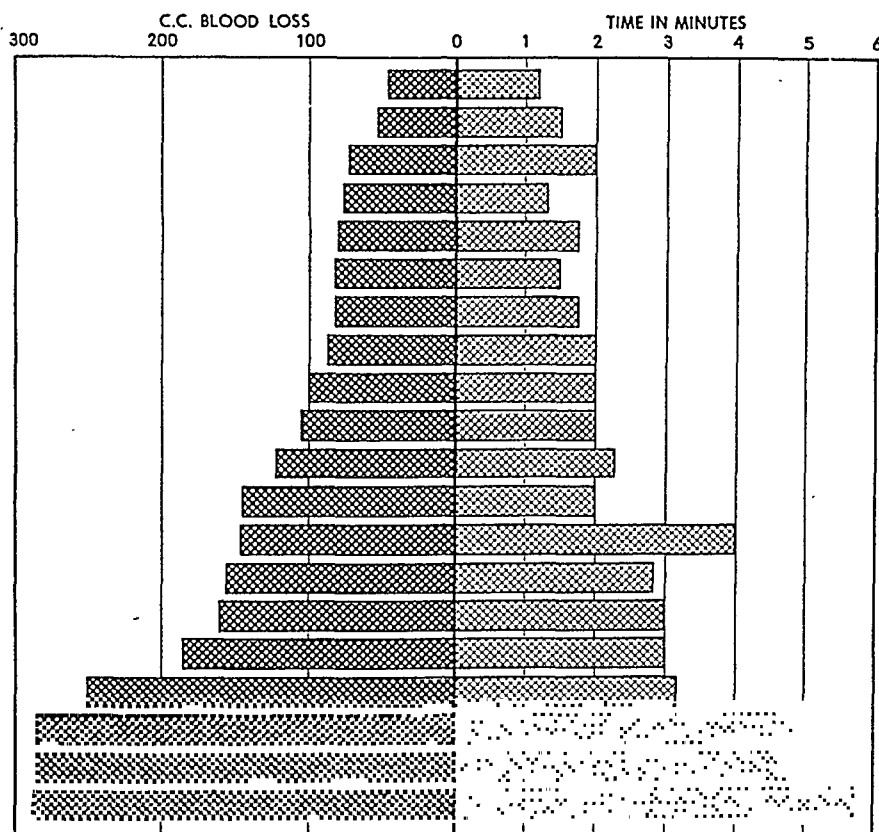


Fig. 2.—Episiotomy blood loss. Relationship between elapsed time and blood lost during first phase.

Summary

Following left medial lateral episiotomy, the amount of blood lost is directly related to time: the time consumed between the incision and the tamponade of the wound by the infant's head. And this period has been designated as phase one. The use of a stuffed sponge in episiotomy wounds does not significantly reduce blood loss per minute during phase one when compared with those cases where no tamponade is used. Ligation of bleeding vessels will reduce the blood lost per minute (during the first phase), but the total blood loss becomes increased because of the time consumed. Total blood loss during phase one can be significantly reduced by shortening the time for that period. In addition, the episiotomy blood loss per minute during outlet forceps delivery, or after the application of thrombin to the wound, is less by comparison with that during low forceps (without tamponade).

Phase two, that period of actual delivery, is without significant bleeding.

During the third phase, that period after delivery until completion of the episiotomy repair, the rate of bleeding is much less by comparison with phase one. This rate is less following slow than following more rapid delivery. The mechanism for the reduced rate of bleeding during phase three is explained.

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FERTILITY IN WOMEN: THE LENGTH OF TIME REQUIRED TO CONCEIVE

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CIRCUMSTANCES associated with potential transfer of husbands in the armed forces during World War II motivated many married couples to begin a family.¹ When pregnancy failed to occur within a few weeks or months they often assumed themselves sterile, or that their technique of union was incorrect. Women falling into this category composed nearly 5 per cent of the patients who sought obstetric and gynecologic consultation at the U. S. Naval Hospital and U. S. Naval Station, Key West, Florida, from May 15, 1942, to July 1, 1944. Many of these individuals were not informed on the physiology of reproduction. On the other hand, the consultants found little reliable information to answer the question regarding the average time required to conceive. To contribute further information to this problem is the purpose of this paper.

Clinical Material

The patients were wives of Naval, Marine Corps, or Army personnel, seen by the authors at the U. S. Naval Hospital, Key West, Florida, between Feb. 15, 1943, and June 20, 1944. Their ages ranged from 16 to 42 years. The average age was 24 years for the primigravidas and nulligravidas, and 26.7 years for the multigravidas. The figures compared favorably with Pearl's statistics² of 23.4 and 23.18 of the United States Birth Registration Area for 1930.

Out of nearly 1,600 women seen for obstetric or gynecologic consultation, 1,192 were selected for study. Those excluded either had some physiologic or pathologic condition precluding pregnancy; became pregnant out of wedlock; became pregnant while using contraceptive measures; were using contraception satisfactorily; or data for them was totally inadequate. Of those to be studied, 799 were pregnant and 393 were not. None used contraception. For purposes of analyses, the 1,192 were divided into three categories: Group I was composed of 318 obstetric patients selected at random. Pertinent data were available for all these. The remaining 481 pregnant women formed Group II. For these, coital rates were unknown, and 20 to 25 per cent had been separated from their husbands for periods of one to twenty-four months. Information for the 393 nongravid who constitute Group III was comparable to Group II. Among Group I were 261 primigravida and 57 multigravida. Corresponding figures for Group II were 354 and 127. The nonpregnant were made up of 251 nulligravida and 142 gravida i or more.

From each woman the date of marriage; past, marital, and family histories; rank or rate and age of the husband were obtained. All had a pelvic examination and nearly all had a complete physical and laboratory study including urinalysis, red blood count, and blood serology. In addition, one physician

(A. W. D.) questioned those in Group I individually at some time during pregnancy to determine coital rates. The frequency of sexual intercourse during the month prior to conception was accepted.

Permanent addresses given covered the 48 states. All but two women were white. Approximately 25 per cent were wives of officers, while the remainder were spouses of enlisted men. All dependents lived on an island five by one to two miles in size. Geographic description of the area has been given elsewhere.³

The husbands ranged in age from 18 to 49 years, with the average of 27.5 years. On the average, they were away from home one night out of three. It should be recognized that these men were picked because of their physical fitness for the Armed Forces. Therefore, they are a select group as compared to the population at large.

Results

Among Group I, 190 of the primigravidas conceived within six months, 226 in twelve months, and 249 in twenty-four months. Corresponding figures for 57 multigravidas were: 22, 37, and 49. See Table I.

Fifty-nine of the newly married women became pregnant immediately after marriage and before having another menstrual period. The fruitful intercourse in all these women, except one, occurred before the end of the third quarter of the menstrual cycle. The time of marriage with reference to the first day of the last menstrual period was: 39 seven to ten days afterwards; 13 in two weeks; 6 in three weeks but 7 to 10 days before the next expected menses; and 1 five days before the next expected menses.

From Group II, 160 of the primigravidas were pregnant in six months; 257 in twelve months, and 312 in twenty-four months. In order, the figures for the multigravidas were 16, 49, and 89. Interestingly enough, a large proportion of the pregnancies that began after eleven months did so at twelve, twenty-four, thirty-six, forty-eight, and seventy-two months (79 out of a possible 172). Transfer of personnel in the Navy was made generally at 6-, 12-, 18-, or 24-month intervals. The figures suggest pregnancies might have followed shortly after reunion of husband and wife. The same observation was made among 108 pregnant women not included in the study. These individuals were using contraceptive measures up to a short time before conception occurred. On the other hand, forewarned of a separation, these couples may have decided to produce a pregnancy.

TABLE I. LENGTH OF TIME REQUIRED FOR CONCEPTION TO OCCUR AMONG 799 MARRIED WOMEN

| GROUP | PATIENTS NUMBER | 6 MONTHS PATIENTS | | 12 MONTHS | | 24 MONTHS PATIENTS | | NO. NOT PREGNANT IN 24 MONTHS |
|---------------|--------------------|----------------------|----------|-----------|----------|-----------------------|----------|-------------------------------------|
| | | NUMBER | PER CENT | NUMBER | PER CENT | NUMBER | PER CENT | |
| Primigravidas | | | | | | | | |
| I | 261 | 190 | 72.7 | 226 | 86.6 | 249 | 95.4 | 12 |
| II | 354 | 160 | 45.2 | 257 | 72.6 | 312 | 88.6 | 42 |
| Multigravidas | | | | | | | | |
| I | 57 | 22 | 38.5 | 37 | 64.9 | 49 | 86.0 | 8 |
| II | 127 | 16 | 12.5 | 49 | 38.5 | 89 | 70.1 | 38 |

One hundred and thirty-eight (54.9 per cent) of the nonpregnant nulligravida were not pregnant by the end of eleven months, while the other 113 (45.1 per cent) had not conceived after twelve to seventy-two months or longer. Corresponding figures for the previously gravid patients were 39 (27.4 per cent) and 103 (72.6 per cent).

Coital rates (Table II) were comparable to those reported by Davis.⁴ The impression was gained that an average of two or three coitions per week were attained in six to twelve months after marriage. There was no obvious relation between frequency of union or age of patients and time required to conceive.

Comment

In most instances, previous communications on the subject of fertility rates have been based on analysis of hospital records where emphasis usually had been directed to problems other than the time required for conception. Also, many of the case studies were gathered by numerous individuals so that questioning was haphazard. The patient was often required to depend on memory to recall facts five to ten or twenty years past. The unreliability of the human testimony vitiates the results.⁵ Some of the observations recorded in this survey may be subject to the same criticism. However, an attempt was made to minimize

TABLE II. AVERAGE NUMBER OF COITIONS PER WEEK AMONG 318 PREGNANT WOMEN IN THE MONTH PRIOR TO CONCEPTION

| FREQUENCY OF COITUS PER WEEK | PRIMIGRAVIDAS* 261 SUBJECTS | MULTIGRAVIDAS† 57 SUBJECTS | DAVIS ⁴ 971 SUBJECTS |
|---------------------------------|--------------------------------|-------------------------------|------------------------------------|
| 1 to 2 | 105 | 45 | 391 |
| 2 to 3 | 124 | 11 | 305 |
| Four or more; less than 7 | 20 | | |
| Less than once | 1 | 1 | 125 |
| Exact data not given | | | 60 |
| Daily or often | 11 | | 90 |

*Four patients were above the age of 30 years.

†Nine were above 30 years.

inaccuracies by basing the questions on recent events and limiting the number of examiners to three. The ideal plan would be to have each newly married woman keep detailed records over long periods of time.

Many variables influence fertility: libido, coital rates, frequency of occurrence of pregnancy in relation to the physiologic possibility, contraceptive measures employed, if any, reproductive wastage, and availability and viability of ova and sperm in the female genital tract.

Libido is indirectly estimated by the frequency of sexual intercourse. The frequency of sexual contact may vary considerably with the age of the couple, with the duration of marriage, the amount of other physical activity endured, and the desire to have offspring. Although husbands were not home every night, it is believed that the temporary absences added to rather than detracted from sexual ardor. At least it is questionable whether sexual relations would have been significantly more frequent with the couple living at home continuously. The factor of climate may have played a part in Key West. Those going to torrid from more temperate zones have a temporarily accentuated sexual activity.⁶ Outdoor workers are supposed to be more active sexually than those occupied indoors, and laborers more than professional people.² The clientele of this study received maximal amounts of fresh air, but were usually not as physically active as a day laborer.

Although coitus was more frequent in early marriage, it is noteworthy that the average patient did not become pregnant for a matter of months. The same idea has been confirmed by Stix and Notestein.⁷ Our figures approximate more nearly those recently reported by Russell⁸ than those given by Pearl. The former found among 197 first conceptions and 96 second conceptions nearly two-thirds of the pregnancies started within three months following natural coitus, while the latter's corresponding percentage was over one year. The mean number of months before pregnancy began plotted against the various frequencies of coitus gave a similar product. Stix and Notestein give a partial explanation on the basis that complete entry may not be accomplished the first few weeks. Williams⁹ and Moench,¹⁰ in addition, have shown that excessive sexual activity on the part of the male may detract rather than enhance conception. It is probable that an ovum does not live more than twenty-four hours, and sperm are capable of fertilizing only twenty-four to seventy-two hours.¹¹ Theoretically, a normal woman can become pregnant only one to three days each month.¹² Generally, women are physiologically sterile for an average period of three months after delivery because ovulation does not occur.^{13, 14} Therefore, the apparent sterility of a parous individual as compared to a primigravida is relative. Coitus at the average rate of 2 to 3 times per week would many times fail to coincide with ovulation. In other words, the important thing is when sexual union occurs, not how often.

Summary

From a survey during 1943 and 1944, of 318 pregnant (261 primigravidas and 57 multigravidas) married, white women ranging in age from 16 to 42 years, and living in a semitropical climate with husbands who were members of the Armed Forces, and away from home one night out of three, it was found that 86 per cent of the primigravidas conceived in the first year of married life. The corresponding figure for 57 multigravidas was 64.9 per cent. Contraception was not employed by these couples. Sexual union was experienced more or less by chance with relation to the time of ovulation, but on an average of two to three times a week.

Although all data were not available for 481 other pregnant and 393 non-pregnant women, using no contraception, results collected therefrom, correlated with those above, substantiate the conclusion that the majority of fertile couples can expect pregnancy to begin within twelve months after marriage. Multigravidas will require a slightly longer time to conceive than primigravidas because there is a period of relative sterility following the previous pregnancy.

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THE ROLE OF NUTRITION IN PELVIC VARIATION*

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VARIATIONS in the shape of the adult female pelvis have a major interest to obstetricians because roentgen studies have shown that even in healthy adults there exists wide differences in pelvic architecture. Furthermore, some of these so-called "normal variations" may have a decided influence on labor and their delineation before that event often reveals highly useful information. The present communication is concerned chiefly with an inquiry into the reason why these variations occur and why the childhood type of pelvis, i.e., dolichopellism, is preserved in enlarged form in some adults but not in others. It presents evidence that, among other factors, nutrition, especially during the puberal period of growth, apparently plays a major etiologic role.

Approach to the subject is best served by considering certain facts concerning the shape of the pelvis in infancy and childhood. The shape of the pelvic inlet in early childhood in both sexes is characteristically elongated anteroposteriorly, or *dolichopellic* (Fig. 1), and if a pelvis of this type were to grow symmetrically it would have a similar shape in adult life. From this it would appear that the round or flattened forms of the adult pelvic inlet may arise as a result of either of two mechanisms; an excessive growth laterally, that is, of the transverse diameter, or a diminished growth anteroposteriorly. From studies of the author and associates, it seems apparent that the lessening or incomplete development of the anteroposterior diameter is the more important mechanism, increasingly so as the degree of flattening becomes more extreme.

For purposes of classification we may say that the tendency of a pelvis to retain most of the relationships of fetal and childhood conformation and thus remain relatively elongated anteroposteriorly may be spoken of as *dolichopellism* (*dolicho* = long), while the tendency in a pelvis to become broadened transversely and short anteroposteriorly is that toward *platypellism* (*platy* = broad or flat). A simple and useful classification of pelves, therefore, can be based upon these anteroposterior and transverse pelvic relationships, as suggested by Turner in 1885.¹ The relative size of these two dimensions is most conveniently expressed as the pelvic index. This index is the anteroposterior diameter of the pelvic inlet times 100 divided by its maximum transverse diameter. By means of this index it is possible to group together pelves which show the same degree of anteroposterior flattening or elongation regardless of their absolute size. Turner classified pelves into three types on the basis of

*This study was made possible through grants from the Clinical Research and Teaching Funds of Yale University School of Medicine.

their pelvic index. Those with an index of 95 or more he called dolichopellic, those with an index from 90 to 94.9 mesatipellic, and those with an index less than 90 he termed platypellic. For anthropologic purposes the use of the pelvic index is ideal and would be useful in clinical evaluation, except that it is a little unwieldy because it cannot always be estimated by simply viewing dimensions.

A simpler and more useful plan for classifying pelves based upon the principle of the "pelvic index" follows. In this method pelves are divided into four general groups:



Fig. 1.—Dolichopellicism in pelvis of child of 3 years (female). Anteroposterior of inlet, 6.1 cm.; transverse of inlet, 5.5 cm.

1. *Dolichopellic type*: The anteroposterior diameter of the inlet is longer than the transverse.
2. *Mesatipellic type*: The anteroposterior and transverse diameters of the inlet are equal or the transverse diameter is no more than 1 cm. longer than the anteroposterior.
3. *Brachypellic type*: The transverse diameter is more than one and less than 3 cm. longer than the anteroposterior diameter.
4. *Platypellic type*: The transverse diameter is 3 cm. or more longer than the anteroposterior diameter (Fig. 2).

We have found this method of pelvic classification clinically useful as a ready means of identifying pelves for purposes of description and record. For purposes of completeness, certain morphologic characteristics, not associated with mensuration, may be added to the pelvic survey, such as the width or narrowness of the pelvic forepart, sacrosciatic notch, etc.

From our investigations of adult pelves in both sexes, it appears that at the present time methods of classification based on sex characters may be confusing and in some instances not altogether sound. This is in view of the fact that our studies in male pelves show essentially the same variations that we find in the female.

Thus, in the investigations of Gruelich and the author² we state, "Our findings indicate that the pelvic inlet of the male is as variable in shape as that of the female. . . . It is evident, therefore, that there is in our population at least no one type of male pelvis, just as there is no one type of female pelvis." And again, "It is evident from the tracings that the shape of the pelvic inlet of most of the men of our series is quite different from that described in the textbooks as typically masculine. Indeed, the pelvic inlet of some of our males so closely resembles that of some of the student nurses of our earlier series that it would be difficult in certain cases to determine the sex of the individual from the shape of the pelvic inlet alone."

It seems clear that, while certain sex characteristics of male and female pelves can be accepted as more or less constant, others formerly thought to be constant are highly questionable. Added to this is the fact that "normal" variations in anteroposterior and transverse relationships are apparently present in both sexes in wide distribution. That the anteroposterior and transverse relationships can form a suitable basis for clinical classification has been recently re-emphasized by Nicholson,³ who states: "Obstetricians have of late devoted a great deal, probably too much attention to the classification of the pelvis by its shape. Accepting the fact that the lengths of the pelvic diameters, in common with other anatomic measurements, are normally distributed, we may from the given figures calculate the corresponding figures for the pelvic index which after all is the chief guide to the shape of the pelvis."

TABLE I. INCIDENCE IN 107 YOUNG GIRLS

| AGE | NUMBER OF CASES | DOLICHOPELLIC (%) | MESATYPELLIC (%) | BRACHYPELLIC (%) |
|-----|--------------------|----------------------|---------------------|---------------------|
| 5 | 2 | 100.0 | | |
| 7 | 1 | 100.0 | | |
| 9 | 4 | 75.0 | 25.0 | |
| 10 | 25 | 72.0 | 28.0 | |
| 11 | 21 | 86.0 | 14.0 | |
| 12 | 18 | 50.0 | 33.3 | 16.7 |
| 13 | 14 | 35.5 | 50.0 | 14.5 |
| 14 | 18 | 27.8 | 55.5 | 16.7 |
| 15 | 4 | 25.0 | 75.0 | |

TABLE II. INCIDENCE OF PELVIC TYPES

| | 100 NURSES (%) | WHITE 1,100 "CLINIC" WOMEN (%) | 100 NEGRO WOMEN (%) | WHITE 107 CHILDREN (%) |
|---------------|-------------------|---|---------------------------|------------------------------|
| Dolichopellic | 37.0 | 18.6 | 29.0 | 59.9 |
| Mesatipellic | 46.0 | 49.9 | 43.0 | 33.6 |
| Brachypellic | 17.0 | 32.2 | 25.0 | 8.3 |
| Platypellic | -- | 3.2 | 3.0 | -- |

Some idea of the distribution of these types in several groups of our population may be gathered from the statistical information gathered through roentgenologic studies by the author and associates⁴⁻⁶ shown in Tables I and II.

Our knowledge of the influence of endocrine forces on pelvic architecture may be aided by certain observations found in a report on Mental and Physical Growth in Pubertas Praecox published in 1939 by Gesell, Thoms, Hartman,

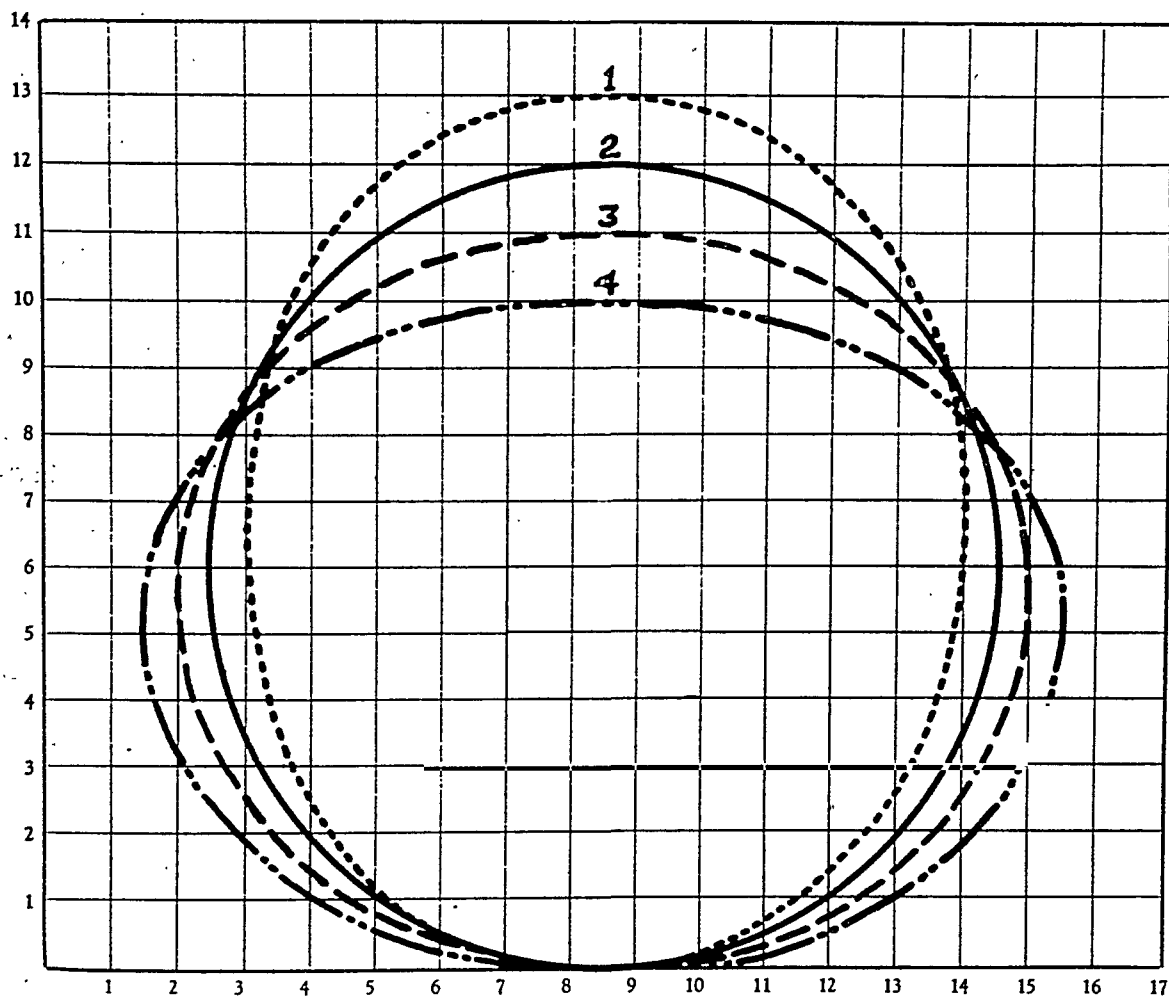


Fig. 2.—Diagram showing usual pelvic variations in four groups. (See text.)

and Thompson.⁷ This report was based primarily upon fifteen years of observation of a patient with a well-defined, uncomplicated pubertas praecox who showed signs of pubescence in the first year of life and menstruated at the age of 3 years and 7 months. She died at the age of 18 years and 7 months of an infection following the removal of a cerebellar fibrillar astrocytoma. Growth in height practically ceased at the age of 11 years. At the age of 18 the pelvis was of a typical dolichopellie type and posteriorly exceptionally spacious. Dolichopellism was not extreme, the pelvic inlet being well rounded in both forepart and hindpart, the measurements being anteroposterior diameter 12.00 cm., transverse diameter 11.25 cm. If the oval or brachypellie type pelvis results chiefly from sex hormone influence, it would be fair to assume that in this case a marked tendency toward platypellism should be present.

This raises the question as to whether the oval or brachypellic type pelvis may not be the result of certain deficiencies in nutrition, especially during the puberal period when nutritional requirements seem to be in more delicate balance than at other periods of growth. In a recent statement, Johnson⁸ stated, "The margin of safety to insure storage (of calcium) in girls at puberty is small . . ." and, "The comparative rarity of clinically recognizable rickets beyond infancy may account for the casual attitude of the average pediatrician toward adequate provision of calcium and vitamin D." The question suggests itself, may not these relatively flattened pelves (brachypellic, platypellic) be the result of calcium imbalance, slight rickets if you will, during the puberal period when the demands of skeletal growth are so increased?

The rachitic pelvis, resulting from severe types of rickets, is well known. It is manifested chiefly by marked platypellism, and in some cases the deformity is so great as to greatly shorten and almost obliterate the anteroposterior diameter. Anteroposteriorly such a pelvis seems collapsed upon itself, the so-called osteomalacic pelvis.

Flattening of the pelvis, either to a mild or severe degree, could occur as a result of one or two mechanisms or both, namely, as the result of mechanical force, i.e., weight bearing, or differences in the rate of growth under rachitic influence of certain portions of the pelvic bones. An investigation along these latter lines by the author⁹ in 1936 was entitled, "Is the oval or female type pelvis a rachitic manifestation?" This paper, therefore, raised the question as to whether the oval or brachypellic type pelvis, so long regarded in anatomic and obstetric texts as the "normal female pelvis," was not in reality abnormal, and the mesatipellic and dolichopellic types, because of their greater combined incidence, essentially "normal" types. Furthermore, because the writers of such texts apparently were unaware of the existence of these latter types, "the predominant type of pelvis which was formerly seen in clinics may have actually changed in character within a generation. When alterations are considered in environment surrounding female infants and adolescent children during the past twenty-five years, changes brought about not only by a great difference in diet, but by such influences as outdoor exercise and life in the open, it must be admitted that the environment for this group has changed indeed during that period. When one further considers the sedentary habits, the type of clothing, the diet, and general restrictions that previously were a part of the life of female infants and children, may one not speculate as to the effect of such an environment on the adult form of the female pelvis? That changes in environment can effect skeletal changes in a large proportion of a population is witnessed in recent years by the extraordinary lessening of the incidence in children of severe rachitis." Further evidence which would suggest such changes is found in the statement of Hooton,¹⁰ who says, "Nearly everyone knows that Americans are getting taller, generation by generation," and the studies compiled by Riggs¹¹ showing the significant increase found in the statures of entering freshmen in the northeast, midwest, and northwest.

The author's communication on the oval pelvis was based on a study of the pubic and iliac portions of the *line of terminal length* in the pelves of fifty women. The terminal length theory of Breus and Kolisko¹² may be briefly stated.

These authors maintain that the relative flattening of the superior strait in the adult pelvis is due not so much to mechanical forces, but to differences in rate of growth before puberty of certain portions of the pelvic bones. They pronounce particular importance upon the so-called terminal length of the innominate bone. They point out that if we saw through the innominate bone at the level of the iliopectineal line and view the sawn surface of the upper half, we shall see that the surface may be arbitrarily divided into three parts, the sacral, iliac, and pubic portions. These are practically of equal length, the whole being in the neighborhood of 20 cm. In the period of development these portions arise from the following: the sacral-portion from the cartilage of the iliac crest, the iliac portion from the Y-shaped cartilage of the acetabulum, and the pubic portion from the same cartilage and from that of the symphysis. These authors contend that the variations in the rate of growth of these three portions are the most important factors in determining the shape of the pelvis and that mechanical factors play a distinctly minor role.

They further state that in rachitis the pubic portion retains its normal proportions, the iliac portion being greatly shortened, and the sacral portion slightly shortened. When this change is present, they state that it is almost pathognomonic of rachitis." This roentgenologic study of 25 oval (brachypellic) and 25 mesatipellic and dolichopellic pelves showed that in nearly all instances the iliac portions in the former were from 1.00 cm. to 2.25 cm. shorter than the pubic portions. The paper concluded thus, "From available information concerning pelves in aboriginal people living in climates in which rachitis does not occur, it appears evident that the round type pelvis is greatly predominant. Furthermore, it seems apparent that the unusual incidence of the round and the anthropoid types in the women of our population must be explained on grounds other than those based on such influences as race and constitution. The above study would appear to be important evidence toward a definite answer to this problem."

In a paper entitled, "What Is a Normal Pelvis," published in 1934, the author¹³ presented the views of other observers which are appropriate to the present discussion and are here restated.

"Stoney and Vaughan have suggested that oval pelves are not truly the result of racial influence but are caused by the conditions of life in modern civilization. The former says that the oval pelvis of the civilized woman is due to lack of light and vitamin D. Vaughan emphasizes the causal relationship of other factors such as posture (especially in children) and points out that differences in pelvic development may be noted in the same race living under different conditions. Thus, women of India and China who work outdoors have easy labors, while those living in cities or in seclusion have difficult labors. Jarcho quotes the Carnegie Trust Report for 1917, which emphasizes the 'easy labors and large families among the Highland women who, barefooted, haul in the nets with the men, follow the plough and engage in field work.' Incidentally, I may add that their diet probably consists largely of fish, which is a well known source of vitamin D.

"The effect of civilization on an aboriginal people living under poor hygienic conditions in large cities is nowhere better shown than in the studies of J. Whitridge Williams, who emphasizes the effect of such an environment

in producing 'rachitis and imperfect general development which play so conspicuous a part in the genesis of abnormal pelves in the colored race.'

"Miller, in speaking of Williams' studies of rachitic pelves in the Negro women of Baltimore, makes the comment that he (J. W. Williams) works in a city which is essentially Northern in mode of life and his patients live in tenements and in typical tenement surroundings, whereas the Negro of the far South, both in the city and the surrounding country, whatever else he may lack has an abundance of fresh air and sunshine, the two arch enemies of rachitis. Levey's report from the Touro Clinic I might add, corroborates these findings as to the relatively small percentage of contracted pelves among colored women in this part of the country."



Fig. 3.—Child at 3 years, 3 months showing classic signs of rickets.

A recent study by Dunham and the author¹⁴ on "Effects of Severe Rickets in Early Childhood on Skeletal Development in Adolescence" shows that early childhood rickets may or may not leave evidence in the matured pelvis. Our summation of findings was,

For ten children in whom a condition diagnosed as severe rickets had been present in early childhood pelvic roentgenograms were made during

adolescence. On the basis of the pelvic diagnosis, these ten children fall into two groups: five children who had rachitic pelves in adolescence and five who had nonrachitic pelves.

What evidence is there of a relationship between the early histories of these two groups of children and their status in adolescence?

In regard to the age when rickets was known to be active, it was found that of the five adolescent children who had rachitic pelves three were more than 4 years of age when active rickets was diagnosed; of the five whose pelves were normal four were less than 3 years of age when active rickets was diagnosed. *Apparently, the older the child at the time when active rickets of a moderate or severe degree is present, the greater is the chance that the pelvis will show rachitic deformities in adolescence.*

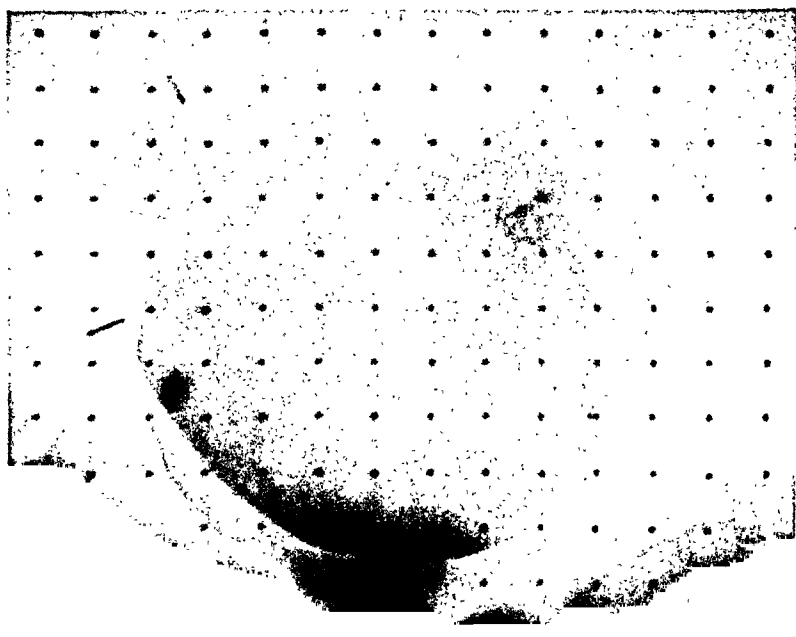


Fig. 4.—Pelvic inlet roentgenogram of child shown in Fig. 4 taken at age 19 years. Typical rachitic pelvis: anteroposterior 7.8 cm., transverse 11.5 cm. (Note shortening of iliac portion—line of terminal length.)

In regard to physical development in early childhood, as indicated by the age at which the children were able to sit and to stand, no striking differences were found in the two groups. All the children were able to sit alone before they reached 1 year of age, and three children in the group with rachitic pelves and two in the group with nonrachitic pelves did not walk until they were 2 years of age or older.

Physical examinations showed that all ten children had in adolescence some deformity of the lower extremities. In the children who had had severe rickets in early childhood knock-knees were associated more often with rachitic deformities of the pelvis than were bowlegs.

Severe or moderate deformities of the spine or of the lower extremities were found in early childhood as often in the group with normal pelves in adolescence as in the group with rachitic pelves. Differences in the two groups

were found, however, in the incidence of knock-knees in early childhood: of the five children with rachitic pelves in adolescence two had had knock-knees in early childhood and two had had bowlegs (the status of one was not known). Of the five children with normal pelves, none had had knock-knees in early childhood. These observations suggest that if knock-knees were present in early childhood the pelvis in adolescence is more likely to show the deformities of rickets than if bowlegs were present in early childhood. It is perhaps significant that one of the children who had had bowlegs in early childhood had in adolescence an unusual deformity that resulted in outward curvature of one leg and inward curvature of the other.

As is well known, high ratios of sitting height to standing height are considered evidence of retardation of growth of the lower extremities. High ratios were found for all but one of the children; this observation includes both the children with rachitic and those with nonrachitic pelves. One child with a rachitic pelvis had a normal ratio, and one was not measured.

Further evidence of the influence of environment in pelvic change is seen in "A Study of Pelvic Type and Its Relationship to Body Build in White Women," by Greulich, Twaddle, and Thoms,⁵ in which a comparison was made among 104 student nurses, a much more privileged economic group than that of 582 primigravid white women of clinic status.

The incidence in these groups is shown in Table III.

TABLE III

| | 104 STUDENT NURSES | 582 CLINIC WOMEN |
|---------------|--------------------|------------------|
| Dolichopellic | 37.5% | 15.0% |
| Mesatipellic | 44.2% | 44.8% |
| Brachypellic | 18.2% | 34.3% |
| Platypellic | ----- | 5.6% |

A further comparison "of body build and pelvic type in 132 of the clinic women and the 104 student nurses disclosed the following relationships: (a) The women with long oval pelves were predominantly tall, long headed, and broad shouldered; the width of the pelvis between the iliac crests, and of their hips between the trochanters were smaller in proportion to the width of their shoulders than in women of the other pelvic types; they had the largest average external conjugate diameter. (b) The women with transversely elongated pelves were, on the average, the shortest of the series and they had the broadest heads, the narrowest shoulders, the widest pelves and hips in proportion to the width of their shoulders, and the smallest external conjugate diameter. (c) The women with round pelves were approximately intermediate between the other two groups in all these dimensions. There was, however, so much variation in these external dimensions between student nurses and clinic women of the same pelvic type that, in our opinion, it would be quite hazardous to attempt to predict pelvic type on the basis of those dimensions in individual cases in a population as heterogeneous as that of this country.

The high incidence of long oval and of round pelves among the largest women of both groups suggests the possibility that nutritive and other factors

which make for the attainment of maximum normal growth tend to prevent that degree of anteroposterior flattening of the pelvis which has come to be regarded as characteristically feminine.

Evidence of the role which nutrition probably plays in pelvic architecture is seen in a recent report by Allen¹⁵ in a study of 244 New Zealand women, who states that the series is representative of New Zealand-born women of childbearing age in his district, and that there is no reason to suppose that it is not fairly representative of New Zealand-born women as a whole.

In his group he found the following incidence, separated according to Turner's original classification, as follows:

| | |
|-------------------------------|-------|
| Dolichopellic—(index over 95) | 54.2% |
| Mesatipellic—(index 90 to 95) | 18.2% |
| Platypellic—(index below 90) | 27.6% |

His opinion regarding etiology coincides quite closely with the author's, and is here quoted:

"It is interesting to speculate upon the reasons underlying this variation, which is dependent primarily upon the finding that the local pelvis has a relatively and absolutely long obstetrical conjugate diameter. It seems possible that there is more truth in Thoms' suggestion that adequate nutrition can influence pelvic shape than is generally thought. It has been established that until the age of puberty there is very little difference between the shape of the pelvis in the two sexes, but that at puberty the pelvis very rapidly takes on sexual characteristics. It is conceivable that during this period of rapid growth nutritional disturbances might exercise a very profound effect. If these disturbances were to lead to any softening of the bones, the diameter which would predominantly be affected would be the conjugate, because of its relation to the axis of weight-bearing.

"It also appears possible that the responsible factor may be a subclinical deficiency of vitamin D. I discover that this suggestion has already been made by Thoms who regards the oval or female type pelvis as definitely a rachitic manifestation. He quotes the theory of Breus and Kolisko who consider that in rickets there is a pathognomonic relative shortening of the iliac component of the circumference of the pelvic brim. Thoms himself has shown that such a shortened iliac portion is present in the female type of pelvis, and further points out that in aboriginal people living in climates where rickets does not occur, the round type of pelvis predominates. Although, therefore, the statement is commonly made that the round pelvis is normal in Negroes and Hot-tentots and it is implied that this is a racial feature, it is possible that it is due to an anti-rachitic environment.

"The findings here reported lend some support to this theory. The local female almost never in her life suffers from malnutrition of any sort unless for some deliberate reason. The population is rural and semi-rural in type, and dairying is the only major industry. The average per capita consumption of butter for New Zealand as a whole for the last three years (1939-42) is given as 42 pounds per annum, and no doubt it is higher than this locally. The hours of bright sunshine in New Plymouth over the past 31 years have averaged 2,247 per annum. The local female is, therefore, highly unlikely to suffer from any vitamin D deficiency: and, indeed, only two cases of rickets,

both in the same family, have been seen in this district during the last three years. Racial variations can scarcely explain the difference between the New Zealand and English figures, because the local stock is predominantly British, and it is scarcely reasonable to assume that the mere accident of birth in New Zealand could produce such an atavistic reversion in the absence of some environmental factor. I believe, therefore, that the shape of the pelvis is determined more by environment and diet than by inherited racial tendencies."

Another recent study bearing out essentially the same conclusions is that of Nicholson³ who, in a roentgenologic study of the anteroposterior diameter of 640 women in England, makes this statement: "The length of the conjugate diameter is very considerably influenced by nutrition, and, in the absence of any large population which up to now can be considered as fully nourished in childhood, it is still quite impossible to determine the mean to which the measurement tends." Nicholson also states, "Pelvimetry by radiology in 640 cases is analysed to show that the length of the conjugate diameter of the female pelvis is very sensitive to nutrition, and the figure quoted in textbooks of anatomy for this diameter is too low."

In recapitulation these statements are offered:

1. Roentgenography has revealed that the adult female pelvis is subject to considerable variation in its anteroposterior relationships. These variations have a definite clinical interest to the obstetrician, for, in instances they may have a pronounced effect upon the course of labor.

2. The so-called "normal" female pelvis of anatomical texts needs revision because the architecture usually described is that of the brachypellie or oval type, which is present in about only one-third of adult women according to evidence presented here.

3. The pelvis of infancy and childhood in both sexes is essentially similar as far as anteroposterior relationships are concerned; until a time just preceding the puberal period they tend to grow symmetrically. At that time changes in anteroposterior and transverse relationships take place which have been described. These changes are apparently the result of two major influences, sex hormonal and nutritional. It would seem on first appraisal that such hormonal influence was the dominant factor because of the well-known somatic and psychic phenomena associated with the puberal period. Nevertheless, wide variations in pelvic architecture are present in our adult population which are apparently unrelated to such phenomena.

4. Evidence is given to show that nutritional influences during the puberal period seem also to have a major role in these changes in anteroposterior and transverse pelvic relationships, as shown by the studies here presented. This role seems to be associated closely with calcium and vitamin D requirements.

5. The evidence presented here emphasizes the need for further study of the nutritional requirements of the growing child, particularly during the puberal period. It also emphasizes the importance of using that knowledge of this subject which we already have to the end that the nutrition needs of the growing child be met in a manner suitable to the requirements of normal growth.

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ANESTHESIA IN OBSTETRICS*

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IT IS safe to say that analgesia and anesthesia in obstetrics are used much more extensively in the United States than anywhere else in the world. This is fortunate for American women, but the blessing is far from a perfect one. Every year a significant number of babies and many mothers die as the direct or indirect result. In most instances the deaths result from injudicious use, either because the choice of the agent was erroneous, or because too much was used. However, occasionally even when a satisfactory dose of the proper analgesic or anesthetic agent was used a fatality resulted.

By the term analgesia I mean relief of pain, and by the word anesthesia I imply loss of sensation or feeling. There may be general loss of sensation such as that produced by inhalation or intravenous anesthesia or local loss of feeling such as that induced by spinal, caudal, or direct infiltration anesthesia. If loss of consciousness is used as the criterion of anesthesia, then the only anesthetic agents are those administered by the inhalation and intravenous routes. All the pain relievers, including spinal, caudal, and local, would then be called analgesics and not anesthetics. Of course, inhalation agents are both analgesic and anesthetic.

I shall limit my remarks to analgesia and anesthesia used during the second stage of labor and operative deliveries.

The incidence of deaths which occur under practically all types of anesthesia is not generally known. In 44,894 anesthetics given at the Wisconsin General Hospital by well-trained anesthetists, Waters and Gillespie reported 47 deaths, an incidence of 0.1 per cent or one death for about every thousand cases. Gillespie reported 227,546 collected cases of anesthesia with a death rate of 0.12 per cent, practically the same as that among the Wisconsin series.

The anesthetics which are used for parturient women are of five types: (1) inhalation, (2) intravenous, (3) caudal, (4) spinal and (5) local, infiltration anesthesia.

I. Inhalation Anesthesia

The inhalation anesthetics which are generally employed are the volatile agents, chiefly ether but sometimes chloroform, and the gaseous anesthetics, especially nitrous oxide and also ethylene and cyclopropane.

1. *Ethyl ether* is the most widely used anesthetic in obstetrics in the United States. The reason for this is most likely the low cost of ether, its low mortality, ease of administration, and wider margin of safety than with most of the other anesthetic drugs. When ether is used for analgesia its effect is primarily psychic, because if enough ether is used to produce adequate analgesia the intensity of the uterine contractions will diminish. The disadvantages of ethyl ether are: induction is slow and excitement is apt to occur; there is slight damage to the liver, especially if associated with anoxemia; the drug irritates

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the respiratory tract and is contraindicated in patients with infection of the upper part of the respiratory tract, pulmonary disease, acidosis, diabetes, or increased intracranial pressure; ethyl ether is inflammable, and heightened depth of anesthesia produces increasing uterine inertia, and considerable nausea and vomiting follow its use.

2. *Divinyl ether* or *vinethene* is a recently discovered saturated ether which vaporizes more rapidly than ethyl ether. Induction of anesthesia can be completed in one to three minutes instead of the ten to thirty minutes required for ethyl ether. Nausea and vomiting are less, and emergence to consciousness is more rapid than with ethyl ether. The disadvantages of divinyl ether are the possibility of hepatic damage, especially if attended by anoxia, and the difficulty of maintaining depth of anesthesia. Sufficient depth of anesthesia for an episiotomy and repair is quickly possible with divinyl ether, but it is not particularly successful for long operative procedures. It should not be used for more than thirty minutes.

3. *Chloroform* is portable, easy to administer, and inexpensive. However, its use is limited in the United States because of its toxic effects on the liver and heart and its weakening effect on the force of uterine contractions.

4. *Nitrous oxide* is used extensively in obstetrics both for analgesia and anesthesia. It is important to avoid anoxia and cyanosis because of the baby. When properly used as an analgesic at the end of the first stage or during the second stage uterine contractions are not weakened. In fact the relief from pain often tends to shorten labor because the uterine contractions seem to be more effective. For total anesthesia from 80 to 90 per cent of nitrous oxide and from 20 to 10 per cent of oxygen should be used. When oxygenation is adequate nitrous oxide has no effect on the child. The chief drawback of this agent is its limited scope of depth. The complications and mortality which have been associated with nitrous oxide invariably resulted from insufficient oxygen. Even a slight degree of anoxia may result in damage to the mother and/or the child. When relaxation is insufficient with nitrous oxide, ether is often added.

5. *Ethylene* is used chiefly in the Middle West. It produces more relaxation than nitrous oxide and has no adverse effects on the heart, liver, kidneys, or lungs. Its disadvantages are the same as those of nitrous oxide, in addition to explosibility and an increase in nausea and vomiting during recovery from its anesthetic effect.

6. *Cyclopropane* produces good muscular relaxation, acts rapidly, is pleasant to inhale, and may be used for both analgesia and anesthesia. Adequate anesthesia for all obstetric procedures may be obtained with it. Adverse effects from it have not been observed on the liver, kidneys, or lungs. Both induction of anesthesia and recovery are rapid. Nausea and vomiting occur with about the same frequency as with ethylene, but are less frequent than with ether. The disadvantages of cyclopropane are its explosibility, a conjectural effect on the heart, the necessity of a complicated apparatus, and a trained anesthetist. Of all the inhalation anesthetics, I prefer cyclopropane.

Effect of Inhalation Anesthetics on the Uterus.—Nitrous oxide and ethylene have little effect on uterine contractions; in fact, it sometimes appears that they strengthen them. When uterine contractions are tumultuous or too acutely painful, nitrous oxide or ethylene anesthesia will often moderate them and actually hasten delivery. All other inhalation anesthetics tend to diminish the strength of the contractions. Chloroform and ethyl ether cause uterine inertia after prolonged use. Light cyclopropane anesthesia has no effect on the uterus, but in the deeper planes it progressively decreases the force of uterine contractions.

Aspiration of Vomiting During General Anesthesia.—One of the greatest hazards of inhalation anesthesia for obstetric patients is the aspiration of vomitus with resultant aspiration pneumonitis. Spaid pointed out that complications from aspiration are most frequent in women in labor. Often the parturients go into labor after a full meal and are further given considerable food and fluids during labor. Should labor be unusually long or difficult, necessitating energy-giving foods, the optimal calories should be supplied by dextrose solutions given intravenously. In this way the patient is ready for general anesthesia. A therapeutic dose of atropine sulfate, given hypodermically when the patient is taken to the delivery room, will usually lessen salivary secretions during the anesthesia. Aspiration of vomitus is serious, as evidenced by the 33.3 per cent mortality in Hall's collected series of fifteen cases.

The incidence of dilatation of the stomach in women in labor is much higher than is usually realized. This atony predisposes to the eructation of massive amounts of vomitus as soon as the protective pharyngeal reflex is lost during general anesthesia. Extremely light "in and out" anesthesia is also conducive to vomiting. Every delivery room should be equipped with an efficient suction apparatus kept ready for instant use. Promptly placing the patient in the Trendelenburg position and suctioning have been lifesaving. Tracheobronchial aspiration by means of bronchoscopy may be necessary. When evidence of gastric dilatation exists, gastric lavage should be used before a general anesthetic is given.

II. Intravenous Anesthesia

Pentothal sodium is an extremely short-acting barbiturate which is now popular as an anesthetic agent, particularly for low forceps deliveries and for cesarean sections. In the latter operations the pentothal anesthesia is withheld until just before the uterus is incised. Local infiltration anesthesia is used up to this point. This manner of administering pentothal sodium safeguards the baby from a too high concentration of barbiturate with a consequent sluggish respiratory response. Intravenous pentothal sodium anesthesia is not satisfactory for spontaneous deliveries. In forceps deliveries and in cesarean sections, done entirely under intravenous anesthesia, the anesthetic should not be given until actual delivery is attempted because of the possible harm to the baby. Therefore, skin preparation, draping, and catheterization must all be completed before anesthesia is begun. This anesthetic may also be used for manual removal of the placenta and for sterilization operations.

III. Caudal Anesthesia (Caudal Analgesia)

Caudal and paravertebral anesthesia in obstetrics were first suggested by Cleland. Continuous caudal anesthesia or analgesia was introduced by Hingson and Edwards. The advantages of continuous caudal analgesia are the absence of general toxicity, complete absence of the sensation of pain during uterine contractions, and no deleterious effect on the baby, except that which may follow a decided drop in the blood pressure of the mother. Caudal analgesia is helpful in cases of toxemia because it produces a hypotension owing to vasomotor block with associated peripheral vascular dilatation. Deaths directly attributable to the procedure have occurred even in the hands of those experienced with the technique. Likewise, nonfatal complications have been reported; among them "near deaths" requiring prompt and energetic resuscitation, local and general infection, intravenous injection of the drug, idiosyncrasy, injury of the nerve roots, breaking of a needle, precipitous drop in blood pressure sufficient to produce shock (occasionally with disastrous results for

the baby), cessation of uterine contractions, and the necessity for frequent resort to forceps.

In my opinion there is no more satisfactory and pleasant type of analgesia in obstetrics than this procedure when it is performed properly without a mishap. However, because of the definite though slight risk of death and the chance of producing a minor or a major complication, continuous caudal analgesia has a limited field of usefulness. It is definitely a hospital procedure and should be used only in those hospitals which have a personnel large enough and sufficiently experienced not only in obstetrics and anesthesia, but also specifically trained in the use of caudal analgesia. Likewise, this personnel must have the time and the willingness to be in constant and vigilant attendance on women who are given this type of anesthesia. Furthermore, apparatus must be available for instant resuscitation and people trained in its use. Because of possible dangers and complications, the trained personnel and apparatus required and the high cost of this form of anesthesia, there is no need to employ it for the average woman in labor. Most of the pains of labor, which are quickly forgotten anyway, can be relieved by less harmful drugs and anesthetics.

IV. Spinal Anesthesia (Spinal Analgesia)

Spinal anesthesia or analgesia is one of the most dangerous of all anesthetic procedures. Statistical reports indicate that spinal anesthesia suffers by comparison with nearly all other anesthetics.

Dealy found that among 16,273 inhalation anesthetics there were seven deaths, or one in 2,325 anesthetics, whereas in the same hospital among 3,193 spinal anesthetics there were also seven deaths, or one for every 456 anesthetics, hence the mortality following spinal anesthesia was five times as high as that which followed the inhalation anesthetics.

The following statistics based on nearly a million surgical cases were published by Henson. Table I shows that spinal anesthesia has the highest incidence of death. Among the deaths under local anesthesia there was not a single one where $\frac{1}{2}$ per cent novocain was used, and only one death where a one per cent solution was used. All the other deaths occurred with higher concentrations which should never be used, or with nupercaine or cocaine.

TABLE I. (ARRANGED FROM HENSON)

| ANESTHETIC | NUMBER OF CASES | INCIDENCE OF DEATH |
|---------------|-----------------|--------------------|
| Ethylene | 31,426 | 0 per 100,000 |
| Local | 146,970 | 11 per 100,000 |
| Nitrous oxide | 188,820 | 13 per 100,000 |
| Cyclopropane | 12,707 | 15 per 100,000 |
| Ether | 513,560 | 15 per 100,000 |
| Chloroform | 3,842 | 25 per 100,000 |
| Spinal | 91,263 | 42 per 100,000 |
| Total | 988,588 | |

Table II also shows that spinal anesthesia is more dangerous than most other anesthetic procedures.

The risk of death is not the only serious drawback of spinal anesthesia. The incidence of pulmonary complications in high spinal anesthesia is at least as great as after inhalation anesthesia. There are a number of reasons for this, including inhibition of the depth and force of respiratory movements during and after operation, increased viscosity of the secretions of the tracheobronchial tree, and the tendency of the patient to remain immobile after operation.

TABLE II. (ARRANGED FROM TRENT AND GASTER)

| ANESTHETIC | NUMBER OF ANESTHESIAS | ANESTHETIC DEATHS | NUMBER PER 1,000 ANESTHESIAS |
|--------------------------|-----------------------|-------------------|------------------------------|
| Local | 13,151 | 0 | 0 |
| Ether | 14,724 | 6 | 0.407 |
| Nitrous oxide | 6,705 | 2 | 0.295 |
| Nitrous oxide with ether | 2,175 | 2 | 0.919 |
| Cyclopropane | 5,744 | 4 | 0.691 |
| Spinal | 5,436 | 6 | 1.10 |
| Spinal with supplement | 930 | 2 | 2.15 |
| Total | 54,128 | 27 | 0.498 |

A toxic effect on the spinal cord and the spinal nerve roots may follow spinal anesthesia. This may be manifested both clinically and pathologically. Davis, Haven, Givens, and Emmett injected the most commonly used spinal anesthetics into the dural sacs of dogs and observed the following changes: a varying degree of inflammatory reaction in the leptomeninges; changes in the ganglion cells of the gray matter of the cord; swelling and fragmentation of the axis cylinders, and signs of degenerative changes in the fiber tracts of the cord. Myelitis and meningitis may result from an infection carried in with the needle or solution, but they may also occur in the presence of a generalized infection that tends to localize at the site of the lumbar puncture. There may be early and temporary effects such as headaches and mild paralysis of the oculomotor and abducens nerve. Late effects may appear months afterward.

Frequently there is a pronounced fall in blood pressure, which may be accompanied by vomiting, restlessness, pallor, cold sweat, weak pulse, shallow respirations, and sometimes unconsciousness. The uterus may fail to relax when this becomes necessary. In more than half the cases high spinal anesthesia retards labor, necessitating operative intervention. This is most likely due to abolition of the sensory phase of the sensory-motor reflex, which normally brings the voluntary muscles into action.

After the drug has been injected into the spinal canal it is beyond control and, if alarming symptoms appear, the cause cannot be removed. This is probably not true when hyperbaric solutions are used. Spinal anesthesia is hazardous in women with anemia and cardiac decompensation. It cannot be used in cases of shock from intraabdominal hemorrhage, abruptio placentae, or other causes.

In spite of some enthusiastic reports on the use of spinal anesthesia in obstetrics, particularly for cesarean sections, a review of the literature should easily convince one that spinal anesthesia is the most dangerous of all anesthetics for pregnant women. In Franken's collected series of 2,088 cesarean sections performed under spinal anesthesia, there were fifteen deaths, or one in every 139 cesarean sections. This is contrasted by Franken with an incidence of approximately one death for every 3,600 operations performed under spinal anesthesia in nonpregnant individuals. Hence, the death rate among the cases of cesarean section was twenty-six times as high as among the nonpregnant patients. Franken attributes the increased death rate in gravid women to two factors: If uterine contractions are present and not relieved by analgesics, the spinal anesthetic may be forced up to the medulla oblongata. Second, the characteristic circulatory changes in pregnancy and the effects of spinal anesthesia on the circulation combine to become particularly dangerous.

Most of the enthusiastic advocates of the use of spinal anesthesia in obstetrics who have been fortunate enough to have had no fatalities have had "near deaths" which have given them anxious and terrifying moments, even

though these moments were brief. Perhaps the recent tendency of confining the anesthetic to the lower regions of the body, the use of smaller doses, the employment of continuous spinal anesthesia and hyperbaric solutions (Sise) which are more controllable will prove safer. But in my opinion it is not justifiable to employ the customary manner of administering spinal analgesia for the delivery of a baby which, after all, is a physiologic and normal function. One may take risks occasionally for men and women who require serious surgical operations, but there is seldom need to subject obstetric patients to the extra hazards of spinal anesthesia, particularly because there are safer methods of anesthesia and analgesia.

V. Local, Infiltration Anesthesia

Practically all surgeons will agree that the safest anesthesia for persons with serious ailments (such as respiratory infections, nephritis, hypertension, severe anemia, diabetes, and other illnesses) is local, infiltration, or block anesthesia. If local anesthesia is the safest for sick individuals, it seems reasonable to conclude that it is also the safest for all who require surgery. As far as I know, there has been no report of the death of a pregnant woman, delivered vaginally or by cesarean section, for which direct infiltration anesthesia with $\frac{1}{2}$ per cent procaine hydrochloride was believed to be the cause. This cannot be said for any other type of anesthetic. Why, then, is not local anesthesia used more frequently than it is in obstetrics? I believe the reasons for this are that most obstetricians are satisfied with the results of inhalation, caudal and spinal anesthesia, in spite of the fatalities and complications which occur. Another is a disinclination or laziness on their part to make use of local anesthesia because they believe that special skill or knowledge is required. This much is certain: nearly everyone who learns the simple technique of giving local anesthesia and uses it a few times becomes enthusiastic about it. Evidence of this is the constantly increasing number of publications on the subject. Further evidence of the fact that direct, infiltration anesthesia can be used extensively is afforded by the figures of the Chicago Lying-in Hospital at which 60 per cent of all the cesarean sections are being performed under local anesthesia and in an additional 15 per cent local and inhalation anesthesia are combined. To date there have been no maternal or fetal deaths or complications which could be attributed to the local anesthetic (Dieckmann). More impressive proof of how frequently local anesthesia can be used is presented by the statistics of the home service of the Chicago Maternity Service. Parasacral block was used 643 times for major operative procedures, and pudendal block and/or local infiltration was used in 2,323 cases (Tucker and Benaron).

The advantages of local, infiltration anesthesia are as follows:

1. There is practically no mortality resulting from this method. The number of fatalities reported in the literature as having occurred after infiltration anesthesia is extremely small and in most instances the drug responsible for these few deaths was cocaine or high concentrations of procaine hydrochloride.

2. There are no pulmonary complications directly attributable to this procedure. It is of special importance in the delivery of women who have pulmonary disorders such as tuberculosis, bronchitis, asthma, and influenza. It is also an advantage in the delivery of women who have eclampsia and pre-eclampsia, because these patients are particularly susceptible to pneumonia. One of the chief reasons for the absence of pulmonary complications is because the lungs are well aerated, not only during delivery or operation, but also afterward. Because of the absence of vomiting during and after operation, there is no danger of aspiration pneumonitis except in the rarely encountered sensitive woman.

3. There are no local or general complications. There are only three possible difficulties that may arise. A needle practically always breaks near the hub. Its full length should never be inserted so that, should it break off, it can be extracted readily. The second possible mishap is the injection of the solution directly into a vein. To avoid this, one should, before injecting the solution into any area, always pull up on the plunger of the syringe to see whether any blood is drawn into the barrel of the syringe. If blood is seen, a new area must be selected for the injection. Furthermore, the needle should be kept in constant slow motion while the solution is being injected. The third, though rare, possible complication is an idiosyncrasy to the drug used, resulting in shock. The usual symptoms are pallor, perspiration, decreasing pulse rate, nausea, vomiting, cyanosis, and convulsions.

4. The technique is simple and may be carried out in a home as well as in a hospital.

5. There are no ill effects on such vital organs as the liver, lungs, heart, circulatory apparatus, and central nervous system.

6. No special knowledge is required. The physician himself carries out the procedure, and therefore he is not dependent on another individual.

7. No special aftercare is required, as is necessary after general and spinal anesthesia.

8. The amount of blood lost is almost negligible because of the pronounced decrease of bleeding in the operative field.

9. There is no interference with the action of the uterus, of the abdominal wall, or of respiration.

10. Postoperative symptoms are rare.

11. Patients may take liquids and carbohydrates before, during and after the operation.

12. There is seldom any need to hurry through an operation; thus more attention can be paid to proper suturing.

13. The tissues must be handled gently; this is advantageous to the patient.

14. There is less wound infection, since local trauma is diminished and the patient's general resistance has not been lowered.

15. Local, infiltration anesthesia is the least expensive anesthetic.

16. Asphyxia of the child, in contrast to that which may occur with any inhalation anesthesia, does not occur.

Local anesthesia has a few limitations. It should not be attempted in women who are high strung and are definitely afraid of being awake during an operation; likewise in those who are unruly or uncooperative because of severe uterine contractions. Before local infiltration anesthesia is to be used, the operator should have an explanatory talk with the patient. The latter should be promised that her eyes will be covered so she will not see anything around her, that the conversation she will hear will not be gruesome or disagreeable, that the rattle of instruments and utensils will be reduced to a minimum and, above all, that, if she feels much pain and so desires it, she may have an inhalation anesthetic. The operator should live up to all of his promises or the patient may lose confidence, become hysterical, and demand an inhalation anesthetic. The chain of local anesthesia consists of the operator, his assistants (including physicians and nurses), the patient, and the local anesthetic. The most important link in the chain is the operator himself. He must first of all be convinced that local anesthesia is the safest and simplest of all anesthetics; he must learn the technique, and, above all, must be willing to sacrifice the extra time and physical and mental effort that operations performed under local anesthesia demand.

The following obstetric operations can be performed under local, infiltration anesthesia: Dilatation and curettage for incomplete abortion, therapeutic abortion, hydatidiform mole, missed abortion, spontaneous delivery, episiotomy and repair, repair of recent and old childbirth lacerations, low forceps delivery, classic or cervical cesarean section, before or during active labor, Porro hysterectomy, anterior vaginal hysterotomy (vaginal cesarean section), and abdominal and vaginal sterilization. Breech deliveries, and rotation of occiput posterior presentations may be performed when parasaclal is combined with local, infiltration anesthesia.

Effect of Anesthetics on the Baby

Local, infiltration anesthesia has absolutely no deleterious effect on the baby. Likewise, caudal and spinal anesthesia do not affect the baby adversely except in the few cases where there is a precipitous drop in blood pressure. On the other hand, the inhalation anesthetics have been responsible for the deaths of some babies. In most cases it is probable that the analgesic drugs given to relieve the pain of the first stage plus the anesthetic administered for delivery caused the fetal casualties; but inhalation anesthetics by themselves have caused deaths of newborn babies. Inhalation anesthetics are particularly dangerous for premature babies and babies whose mothers have diabetes and other complications.

Summary

I have tried to show that whereas anesthesia is a distinct blessing to women in labor, there are dangers associated with every type of anesthetic except direct, infiltration, or block anesthesia. Therefore, every specialist in obstetrics and every physician who has a large obstetric practice should familiarize himself with the simple technique of local anesthesia. Not all women can be delivered under local, infiltration anesthesia, but there is no doubt in my mind that a more widespread use of this form of anesthesia will reduce both the maternal and the fetal mortality and morbidity.

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THE MANAGEMENT OF OVARIAN TUMORS COMPLICATING PREGNANCY*

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TUMORS of the ovary occur most frequently during the childbearing period and their presence is not necessarily a barrier to conception. Löhlein¹⁰ reports 1 in 1,738 cases of pregnancy, and Fleischen⁷ cites 5 in 17,832. These figures make for an average of approximately 1 in 2,500, but this is undoubtedly low. The apparent low incidence is due to the fact that many cases are not observed on obstetric services, and therefore are not reported. Today, with the recognized necessity for prenatal care, it is probable that more ovarian tumors will be discovered early in pregnancy. The term "tumors" is used in this discussion to designate any enlargement of the ovary and not in the strict pathologic sense.

Many pregnancies, in the presence of an ovarian tumor, have an uncomplicated course. Frequently the tumor remains undiagnosed.

The most common complications which may supervene during pregnancy are torsion of the pedicle, intracystic hemorrhage, and suppuration.^{11, 12} Torsion of ovarian cysts is three times more common during pregnancy than in the non-pregnant state, and is particularly prone to occur during the puerperium because of the free mobility of the uterus. Intracystic hemorrhage is usually associated with torsion, but may occur alone. Suppuration may take place with or without torsion, and invariably manifests itself during the puerperium as the result of lymphatic spread of infection from the uterus.

At term an ovarian tumor may obstruct the entrance of the presenting part into the pelvic inlet, or, when the tumor is situated lower down, it may impede descent of the presenting part through the midpelvis. Besides failure of engagement, with possible rupture of the uterus, there exists the possibility of rupture of the cyst into the vagina, into the rectum, or into the peritoneal cavity.

In view of these potential dangers which ovarian cysts impose upon pregnancy, patients in the childbearing age who have ovarian tumors must be properly categorized so that the appropriate treatment can be selected. They fall into one of four groups:

1. Those who are seeking advice prior to becoming pregnant and in whom, on routine examination, an ovarian tumor is found.
2. The pregnant patient in whom an ovarian tumor is discovered during the first trimester of pregnancy.
3. Those in whom an ovarian tumor is discovered during the second trimester of pregnancy.

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4. Those patients in whom the tumor is discovered at or near term, during labor, or immediately post partum.

The woman who is anticipating pregnancy and presents herself for routine gynecologic examination is a problem of particular interest when an ovarian tumor is found. In the light of our present knowledge of the growth potentialities of ovarian tissues, the advice that all tumors regardless of size or location are best removed cannot be accepted today.

The management of the patient with the single small cyst is usually a source of controversy. Accepting the standard that all enlargements of the ovary 5 cm. in diameter or less are small cysts, one will find that 95 per cent of this group are functional cysts.¹³ These cysts are no longer looked upon as part of the complex group of ovarian neoplasms, but simply as enlargements which come about as a result of altered physiological behavior of the ovary.

Only 0.6 per cent of this group of small cysts are malignant, and these as a rule are not found in the childbearing period.

If these facts are borne in mind, each of the patients with a small ovarian tumor must be carefully individualized. The treatment will be guided by the characteristics of the individual small ovarian tumors, a knowledge of their tendency to grow, to undergo torsion, to bleed, to grow bilaterally, or to become malignant. During pregnancy, because of their size, they usually rise out of the pelvis with the growing uterus, and serious mechanical complications during labor are rare.

The patient who has been a sterility problem and in whom all studies are negative, except for the finding of a single ovarian cyst, frequently may become pregnant following removal of a cyst. When possible, enucleation of the cyst, rather than oöphorectomy, is the best procedure.

When single or bilateral dermoids are suspected, surgery is always indicated. Twenty-five to 30 per cent of reported series of ovarian cysts complicating pregnancy were found to be dermoids.^{12, 14} This high incidence is not surprising since 85 per cent of all dermoids are found early in the period of sexual activity. They are notorious for complicating pregnancy by torsion, rupture, or suppuration, and should be promptly removed if diagnosed at a prenatal examination.^{4, 6} Simple resection of the cysts is best when possible.

The patient with endometriosis frequently has bilateral palpable cysts. She usually does not become pregnant.⁵ If she does, treatment is one of expectancy unless disabling symptoms are manifest.

The finding of a single solid tumor of the ovary in the nullipara creates a problem. Regardless of its size, when a solid tumor is suspected, laparotomy and removal of the tumor are indicated. If there is no question about its benignity, simple oöphorectomy should be performed. If the tumor is malignant but has an intact capsule, should the other ovary and uterus be removed? Frequently, the exact microscopic diagnosis cannot be obtained at the time of operation. And it is now recognized that there is not necessarily any relationship between microscopic malignancy and clinical malignancy in ovarian tumors.^{15, 16} It must therefore be left to the judgment of the surgeon and to his knowledge of

the potentialities of the tumor as to what his procedure should be. The best procedure would be to incise the other ovary to search for possible involvement. But this does not exclude the presence of microscopic tumor elements.

If brief, then, the consensus is that if the tumor is single and encapsulated, a conservative oöphorectomy is the best procedure in the young nulliparous woman who is desirous of having a child. The radical operation is reserved for those cases which are outside the age of reproductivity, where both ovaries are involved, or where the patient has already fulfilled her task of childbearing.

The ovarian cyst which is discovered very early in pregnancy is a problem of special interest from an endocrinologic standpoint. In human beings, as indicated by many clinical observations,^{1, 2, 8, 9} it is noted that the integrity of the conceptus is maintained even with removal of the corpus luteum between the sixtieth to ninetieth days of gestation.

Since the ovarian tumor discovered in the first trimester of pregnancy might contain the corpus luteum, it seems wise to delay extirpation of the tumor to some date when the placenta has definitely superseded the corpus luteum. By the sixteenth week of gestation, oöphorectomy rarely entails difficulty.

An inhalation anesthesia such as cyclopropane is the anesthesia of choice because it is delivered with a minimum of anoxia to the patient. Spinal anesthesia is contraindicated because contractions of the uterus are more apt to follow this type of anesthesia than the inhalation drugs. Postoperatively, the patient should be kept well sedated with morphine or one of the opium derivatives for the first forty-eight hours. At this period of gestation there has as yet been little stretching of the abdominal wall, and no difficulty with the healed incision should ensue at term.

Of course, if early in pregnancy an emergency such as torsion of a pedicle or impaction of the uterus below the tumor occurs, then prompt interference is indicated. Before operating, such a patient should receive progestin (at least 5 mg. intramuscularly each day) in the event that the tumor contains the corpus luteum of pregnancy (Table I).

TABLE I. GROUP OF OVARIAN CYSTS TREATED EARLY IN PREGNANCY

| NAME | CLINICAL PICTURE | STAGE OF GESTATION | PATHOLOGICAL FINDINGS | POSTOPERATIVE COURSE |
|--------------------|--|--------------------|---|--|
| M. S. G-I 18 | Signs and symptoms of twisted cyst. Bilateral cysts discovered. Pregnant | 5 weeks | Right serous cystoma Left papillary adenocarcinoma | Uneventful Now 7½ months pregnant |
| L. W. G-I 20 | Left upper quadrant pain during fourth month of gestation—ovarian cyst palpable | 16 weeks | Left ovarian dermoid | Uneventful Spontaneous delivery at term |
| L. W. G-I 20 | Ovarian cyst discovered during first trimester | 16 weeks | Dermoid cyst | Uneventful Spontaneous delivery at term |
| B. P. G-I 28 | Bilateral pelvic masses discovered at fourth month. Right oöphorectomy—resection left cyst | 16 weeks | Bilateral dermoids | Uneventful Spontaneous delivery at term |

The plan for management of ovarian tumors discovered in the second trimester of pregnancy is not much different. Surgery is indicated as soon as the diagnosis is made. At this point any possible endocrinologic deficiencies do not confuse the issue. Single or bilateral cysts can be removed without difficulty. True, a cyst which by this time has undergone repeated torsion may, because of surrounding peritoneal reaction, be adherent to neighboring structures and the omentum.

The discovery of medium and large cysts during the early part of the third trimester calls for temporizing. The fetus is not yet viable, and operation always carries the risk of premature labor and strain on the abdominal wound. Hence, oöphorectomy is unwarranted unless an emergency arises. At term, its handling will then depend upon the location of the tumor and the age of the patient.

When a cyst is discovered at or near term it presents a somewhat different problem. During labor, in the absence of obstruction, delivery from below may be awaited. The cyst may, however, interfere with engagement of the presenting part into the superior strait, or make for dystocia low in the pelvis. Occasionally it can be dislodged. It is indeed a fortunate event if, after placing the patient in knee-chest or Trendelenburg position, spontaneous passage of the tumor into the abdomen occurs. Attempts at forceful displacement are dangerous because of the possibility of rupture with the dissemination of irritating material (dermoid cyst) into the peritoneal cavity. In the instances where the tumor is immobile, the only treatment is elective cesarean section with removal of the tumor at the same time. If at or near term such a cyst is found riding high in the abdomen alongside of the uterus, one might treat the case expectantly, awaiting delivery from below. The mother is thus saved from a cesarean section, which operation may alter her obstetric course in subsequent pregnancies. Such a case, in the elderly primipara, may be subjected to a cesarean section with oöphorectomy at the same time (Table II).

TABLE II. GROUP OF OVARIAN CYSTS REMOVED AT TERM

| NAME | CLINICAL PICTURE | STAGE OF GESTATION | PATHOLOGIC FINDINGS | POSTOPERATIVE COURSE |
|---------------------|---|--------------------|---------------------------------------|--|
| E. S. G-I 22 | Right upper quadrant and right flank pain, seventh month. X-ray showed calcified areas. Cesarean section and right oöphorectomy performed | 40 weeks | Right ovarian dermoid with hemorrhage | Uneventful |
| I. C. G-II 23 | Knowledge of ovarian cyst at time of first delivery. Mass now in cul-de-sac. Cesarean section and left oöphorectomy | 40 weeks | Dysgerminoma, left | Questionable right-sided ovarian enlargement 1 yr. |
| G. S. G-I 30 | Ovarian cyst discovered during last trimester of pregnancy obstructing pelvic inlet. Cesarean section and oöphorectomy | 40 weeks | Dermoid cyst | Evisceration. Died |
| P. M. G-I 20 | Knowledge of ovarian cyst throughout pregnancy. Cesarean section and oöphorectomy | 40 weeks | Dermoid cyst | Uneventful |

The first sign of torsion of the pedicle post partum is an immediate indication for laparotomy. In other cases the ovarian cyst should be removed during the hospital stay because of the possibility of suppuration, especially if a puerperal infection occurs (Table III).

TABLE III. GROUP OF OVARIAN CYSTS TREATED POST PARTUM

| NAME | CLINICAL PICTURE | STAGE OF GESTATION | PATHOLOGIC FINDINGS | POSTOPERATIVE COURSE |
|-----------------------|---|----------------------|---|---------------------------------|
| E. A. G-VIII 24 | First diagnosed as acute hydramnios. Ovarian cyst diagnosed after premature induction of labor and delivery of fetus | 34 weeks | Ovarian cyst with necrosis and hemorrhage | Died of generalized peritonitis |
| M. L. G-II 38 | Signs and symptoms of peritonitis 3 days postpartum. Ruptured appendix diagnosed | 3 days post partum | Bilateral dermoids; one ruptured. Peritonitis | Stormy. Alive and well |
| B. S. G-II 32 | Fever and abdominal pain. Low forceps delivery 17 days previously. Abdominal mass increasing in size. Ovarian abscess diagnosed | 4 weeks post partum | Pseudomucinous cyst. Infected and necrotic | Uneventful |
| M. T. G-II 25 | Tumor diagnosed before pregnancy. Spontaneous delivery. Abdominal pain and fever postpartum. Mass in pelvis | 3 months post partum | Dermoid cyst with hemorrhage and necrosis | Uneventful |

The trend at present has been toward more radical treatment. The size of the tumor often is an important factor in influencing one's judgment. The rules governing extirpation of ovarian tumors in the nonpregnant patient should apply just as well to the ones which complicate pregnancy. In fact, in pregnancy their removal is even more urgent. Solid tumors and bilateral tumors, because of their frequent association with malignancy, should be promptly removed. Bilateral ovarian dermoids can be readily shelled out and small amounts of ovarian tissue which usually sustain ovarian function can be left.

It is stated in the literature that bilateral dermoids complicating pregnancy are rare. Of the 12 cases reported here, seven were found to be dermoids, and in two instances they were bilateral.

The cases considered in this presentation were from the gynecologic and obstetric services of the Beth Israel, French, and Harlem Hospitals in New York City. In some of these cases it was not within the province of the authors to prescribe the therapy. Hence, the management of the case may not correspond with our above outline.

Summary

1. Ovarian tumors are tumors of the childbearing period and may thus complicate a pregnancy.
2. The presence of an ovarian tumor is, as a rule, no barrier to conception.
3. Dermoid cysts are commonly found complicating pregnancy.

4. Torsion, intracystic hemorrhage, and infection are the commonest complications during pregnancy. Torsion and infection are most frequent during the postpartum period.

5. The small ovarian cyst (5 cm.) is usually one of the group of functional cysts and is rarely a cause for concern before or during pregnancy. Larger cysts should be removed when discovered in the nonpregnant patient.

6. All tumors suspected of being solid tumors of the ovary must promptly be inspected. Cases of bilateral ovarian tumors must also be promptly submitted to surgery.

7. Instances of removal of both ovaries during the second and third month with no interruption of the coexisting pregnancy have been reported.

8. The medium-sized and larger ovarian tumors discovered at the onset of gestation may be removed safely during the first trimester of pregnancy under general anesthesia, preferably cyclopropane.

9. Ovarian tumors discovered during the second trimester of pregnancy should be removed at that time. In the elderly primipara, it may be advisable to delay oöphorectomy until term, at which time cesarean section may be done.

10. The cyst which makes for a dystocia problem at term should be removed at the time of the elective cesarean section.

11. Where the ovarian cyst is discovered at term and delivery of the fetus through the natural passages is imminent, the ovarian cyst should be removed soon after delivery in view of the potential danger of torsion and infection.

12. All the criteria which influence the handling of ovarian tumors in the nonpregnant apply equally as well to the pregnant patient.

13. Twelve cases of ovarian cysts complicating pregnancy are reported—seven were dermoids, two of which were bilateral.

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SINISTROPOSITION: A STIGMA OF RELATIVE INFERTILITY

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THE evaluation of fertility is a complex problem. It involves the study of the potency of the male partner, an as yet not fully understood factor of mutual compatibility, and a study of the woman. The investigation of the female must cover not only the mechanical factors of permeability of the passages, but also the endocrine status, normal and pathologic. Included in this phase of the investigation is the hereditary and acquired "constitution." This factor, too often, is not given sufficient consideration in the general estimate. I have repeatedly¹⁻³ drawn attention to characteristics which distinguish the less fertile groups, some of which are general, others local. Among the latter I have quite recently³ recognized a previously undescribed malposition of the uterus, which upon further study appears to be of real significance in the evaluation of fertility in a given individual.

This stigma which I have called "sinistroposition" of the uterus I regard as a stigma of relative infertility. In order to obtain further clarification, I have searched my private records covering the last two years and have studied and analyzed the case histories in which sinistroposition was found. Among these histories there were a few patients who had been observed over the course of years and in whom, for reasons to be discussed later, it was noted that sinistroposition had developed, usually while under observation. I call this type secondary or acquired sinistroposition, in contradistinction to the primary congenital form.

The uterus in these patients is situated to the left of the median line, in most instances cervix and body being in contact with the tissues of the left pelvic wall. The left parametrium is found to be short, the right one correspondingly elongated. The right adnexa are long, the ovary usually in its normal position. The left adnexa in the primary cases are above the fundus and close to the left pelvic wall (Fig. 1).

In all, 83 patients fell into the category of sinistroposition. Of these, 70 are classifiable as primary and 13 as secondary in type.

Primary Sinistroposition

Of the 70 primary conditions, 38 were married, but eight of these couples had practiced contraception throughout their married life. Consequently 30 could be considered from the point of view of fertility or infertility. Of the 30, only one had had children (twins). Four claimed to have had spontaneous abortions, but all of these were early and none of these could be positively identified as antecedent pregnancies. Of the 30 patients, 19 consulted me because of sterility. The other 11 had various complaints, none of which were characteristic.

- 2 had primary amenorrhea
- 7 had menorrhagia metrorrhagia
- 1 had dyspareunia
- 1 had femoral hernia

The remainder of these patients were unmarried, 32 in number. Seven of these were adolescents, under 17 years, while six were between the age of 40 and 46 years. These patients consulted me for various complaints.

| | |
|----------------------------------|---|
| Menorrhagia and metrorrhagia | 7 |
| Amenorrhea | 4 |
| Irregular menses | 6 |
| Hirsuties | 2 |
| Dysmenorrhea | 2 |
| Grave's disease | 2 |
| Abdominal pain | 3 |
| Overweight | 2 |
| Lumpy breasts | 1 |
| Pseudo adrenal cortical syndrome | 1 |
| Question of pregnancy | 2 |

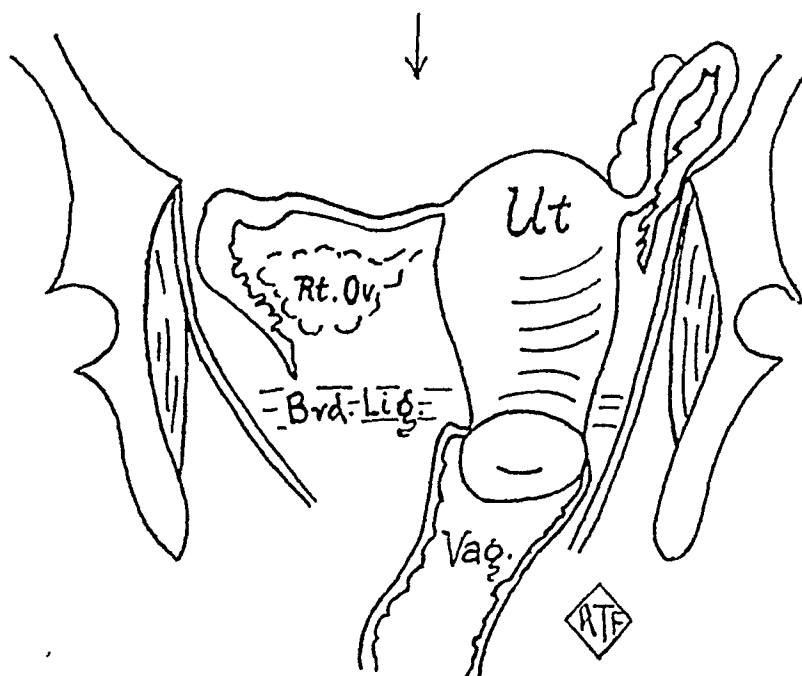


Fig. 1.—Schematic cross section of pelvis showing palpatory findings in sinistroposition of the uterus. Arrow indicates median line.

In my examination I found that 38 of the uteri were either hypoplastic or definitely infantile. In spite of this fact, only 28 of the patients suffered from any dysmenorrhea, and in only two was this actually the major complaint. Another rather striking finding was that in the entire group there were only four retroversions. In the remaining 66, the uterus was anteфлекed. Another rather striking feature was that in only two patients were small fibroids noted. As a group, the patients showed a diminution of basal metabolism, the readings being mainly between -11 and -28 per cent, in the 10 cases in which this test had been made. There were two cases of hyperthyroidism.

On the whole, other endocrine stigmas were not noted in excess to what one finds in an unselected group of patients. There were a few eunuchoid individuals, a few in whom constitutional growth disturbances had occurred, but, in the main, the constitution and build were average normal.

To sum up, the impression made by the group of primary sinistroposition was that this local finding must be considered a congenital malformation which, for as yet unexplained reasons, is encountered mainly in individuals who are or will prove sterile or in the less fertile group. I have no explanation for the de-

velopment of this position of the uterus, although it is noticeable that even in normal individual marked filling of the lower sigmoid loop and rectum crowds the uterus to the left. For this reason, if any suspicion as to a temporary displacement of the uterus existed, these women were re-examined repeatedly after thorough emptying of the large bowel. However, in not one case of the series was the displacement due to an overloaded rectosigmoid. If one's attention is once directed to sinistroposition, one will automatically register these patients subsequently.

Secondary or Acquired Sinistroposition

Thirteen patients were grouped as secondary or acquired sinistroposition. This was done particularly in patients in whom the malposition had developed while under observation. In one patient, 54 years of age, the condition did not develop until after the menopause. This patient had been married twenty-seven years and had never become pregnant. In two younger patients on whom I had performed myomectomies, the malposition developed after operation, evidently due to postoperative contractions. In two patients who had never been pregnant, the condition was noted after operation for removal of left ovarian cysts. In four patients the displacement occurred after prolonged inflammatory episodes with numerous relapses. In two patients deep cervical scars extending into the parametrium had pulled the cervix close to the left pelvic wall. In two patients who had been observed, respectively, for eight and ten years, the condition developed under observation in consequence of chronic inflammatory trouble. In sharp contrast to the primary group, seven of the thirteen patients had had children, and one had had repeated abortions. In four, the malposition can be definitely ascribed to the consequence of pregnancy (two deep tears; two post-abortal inflammatory episodes).

Summary

From these observations it seems justified to conclude that primary sinistroposition is a developmental stigma characteristic of less fertile females. In evaluating the fertility of a given individual, the presence of sinistroposition should be taken into consideration in arriving at a prognosis.

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1035 PARK AVENUE.

THE CAUSES OF DEATH IN CANCER OF THE CERVIX UTERI

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YEAR after year cancer has been responsible for more and more deaths, until, in most States, it ranks among the first three causes of death. In approximately 25 per cent of the women dying from this disease, the lesion is located in the female genital tract, with the cervix as the primary site of the neoplasm in 65 per cent. Unlike most fatal diseases, carcinoma of the cervix per se is rarely the immediate cause of death, most deaths in these cases being due to changes secondary to the original neoplasm. Because very little has been written on this subject and in order to determine just what these causes are, a study was made of the records of 55 patients dying with cancer of the cervix at the University of Michigan Hospital during the past ten years. Complete autopsies, with microscopic examination of all tissues and glands, form the basis of this report.

Symptoms

The most prominent initial symptom among these women had been vaginal bleeding, starting as intermenstrual or postcoital spotting, but gradually progressing in severity. Bleeding persisted and increased to be classed as actual hemorrhage in 71 per cent. Only two patients had no vaginal bleeding. Pain, as a primary complaint, was relatively infrequent, but when it was present it usually occurred in patients in whom the disease was very far advanced.

Type of Malignancy

As indicated in Table I, squamous cell carcinoma of the cervix was the most common type, occurring in 92 per cent. Thirty-eight patients presented medullary squamous cell carcinoma, while eight patients showed the cornifying squamous type.

TABLE I. TYPE OF MALIGNANCY.

| | |
|----------------|----|
| Squamous cell | 52 |
| Medullary | 39 |
| Cornifying | 8 |
| Unclassified | 5 |
| Adenocarcinoma | 2 |
| Sarcoma | 1 |

Associated Diagnosis

In evaluating these patients' records to determine whether or not death was attributable to related medical disease, it was found that no deaths could be directly attributed to an associated medical diagnosis, except in one patient with primary carcinoma of the gall bladder with extensive remote metastases. In this patient the cervical lesion was completely healed and showed no evidence of residual involvement at the time of autopsy.

Clinical Grouping

All patients admitted to our service with carcinoma of the cervix are grouped clinically according to the classification of Miller and Folsome reported in 1938 and their revision of 1945. Eighty-four per cent of this group of 55 patients revealed definite clinical evidence of extension into the parametria, and were therefore in a markedly advanced stage of their disease at the time of admittance.

TABLE II. CLINICAL GROUPING. (U. OF M. CLASSIFICATION.)

| | AT TIME OF ADMITTANCE | AT TIME OF DEATH | | | | | | UNCLASSIFIED |
|------------------|-----------------------|------------------|----|-----|-----|-----|-----|--------------|
| | | I | II | III | IVa | IVb | IVc | |
| Clinic Group I | 0 | | | | | | | |
| Clinic Group II | 1 | | | | 1 | | | |
| Clinic Group III | 8 | | | 2 | | 4 | 2 | |
| Clinic Group IVa | 25 | | | | 18 | 1 | 6 | |
| Clinic Group IVb | 14 | | | | | 12 | 2 | |
| Clinic Group IVc | 4 | | | | | | 4 | |
| Unclassified | 3 | | | | | | | 3 |

The more extensive the clinical involvement, the greater the incidence of interference with vital mechanisms of the urinary tract or alimentary canal. Such interference occurs because the structures carrying on these mechanisms are in the path of spread.

The factors responsible for morbidity were commonly those causing death (Table III). Most patients presented complaints referable first to the urologic tract and second to the gastrointestinal tract.

TABLE III. MORBIDITY.

| | |
|---|----|
| Urologic | |
| Secondary to obstructing carcinoma | 31 |
| Secondary to invading but non-obstructing carcinoma | 5 |
| Gastrointestinal | |
| Intestinal obstruction | 10 |
| Terminal ileitis | 2 |
| Irradiation colitis | 2 |
| Primary gallbladder carcinoma | 1 |
| Pulmonary, from metastatic carcinoma | 7 |
| Peritoneal | |
| Peritonitis | 8 |
| Pelvic abscess | 6 |
| Neurologic | 5 |
| Acidosis | 2 |
| Cerebral | 2 |
| Hemorrhage | 2 |

Causes of Death

In only one case was the cause of death so obscure as to escape explanation. In 40 per cent death was due to genitourinary invasion and/or obstruction. In most of the patients with ureteral obstruction there was also clinical evidence of pronounced urinary tract infection. In most instances obstruction was due to circumscribed, circumferential infiltration and constriction of the ureter. The occlusion, sufficient to cause death, occurred as a result of either periureteral lymphatic invasion by carcinoma cells in the retroperitoneal lymph node chain or by actual invasive spread of carcinoma into the urinary tract itself. With

this obstruction, naturally stasis, hydroureter, and hydronephrosis developed, and, on this basis, secondary infection. The temperature curves of these patients were of a characteristically septic type. When blood cultures were performed among the patients with this type of febrile course, they were repeatedly negative.

Unless there was clinical evidence of infection or destruction due to infection or hydrostatic changes in the urinary tract, supported by the findings on microscopic examination, the diagnoses of pyelonephritis and infected hydronephrosis were not made.

TABLE IV. CAUSES OF DEATH.

| | | |
|--|----|-------|
| Unknown | 1 | |
| Urologic | | |
| Uremia from ureteral obstruction | 11 | } 40% |
| Pyelonephritis from ureteral obstruction | 10 | |
| Pulmonary | | |
| Pulmonary edema | 8 | } 31% |
| Pneumonia from metastases | 7 | |
| Pulmonary embolism | 2 | |
| Gastrointestinal | | |
| Intestinal obstruction | 5 | } 13% |
| Perforation of bowel by carcinoma | 2 | |
| Peritonitis | 5 | |
| Primary gallbladder carcinoma | 1 | |
| Cardiac decompensation | 1 | |
| Spontaneous abdominal ureterostomy | 1 | |
| Hemorrhage | 1 | |

Uremia was the most common cause of death. In practically all cases renal function studies corroborated the diagnosis and supported the pathologic findings. In most of the cases, microscopic examination showed a severe degree of renal deterioration and destruction. Patients in impending uremia or with pronounced degrees of urinary tract infection, in our experience, have not been greatly benefited from repeated ureteral dilatations in an attempt to overcome their ureteral obstruction. Even though ureteral catheterization could be performed readily, pyelography frequently revealed definite ureteral constriction with dilatation above this point. It is for this reason, plus the fact that ureteral tone and amplitude of contraction were lost, that dilatation of the constricted ureter was invariably unsuccessful in relieving this common cause of death. During more recent years nephrostomy has been attended by rather dramatic results in the alleviation of the tremendous distention of the kidney pelvis presented by these patients. There have been instances in the last few years where patients in apparently moribund uremia have responded most surprisingly, and almost immediately, to this method of control. Concomitant with this striking clinical improvement, distinct amelioration in these patients' blood chemistry (often to normal) was attained. Nephrostomy should not be attempted until the dehydration and inevitable acidosis have been combated with proper electrolytes and large amounts of intravenous glucose. We have observed instances where the carbon dioxide combining power has been as low as 11 volumes per cent, and the nonprotein nitrogen elevated to 190 milligrams per cent in patients in deep coma. These patients have been so completely relieved with nephrostomy that they are now carrying on normal activity in reasonably comfortable circumstances. The operation has usually been an emergency procedure, but may be, and should be, elective. When thus electively performed, it is attended by relatively no shock and with small danger. The place of permanent cutaneous ureterostomy, in this group, must await further observations.

Death from pulmonary causes occurred in 31 per cent. While moderate pulmonary edema is common as a terminal manifestation of a generalized septic process, none of the patients here presented showed any true evidence of sepsis. At autopsy the eight patients in this category showed evidence of massive pulmonary edema. There were no pulmonary metastases among the patients dying from extensive pulmonary edema.

Among the patients with pneumonia from metastatic carcinoma, there can be no question that death was due to sepsis, since there was found markedly widespread infiltration by carcinoma with associated secondary necrotic and infectious processes in the lung. All these patients showed evidence of extensive damage to the lung parenchyma, and in most of them the process was so advanced as to produce asphyxia and even compression of the lung. While bronchopneumonia is the most frequent picture found in debilitated and aged individuals, the changes in our patients were those of massive lobar pneumonia. Pulmonary embolism occurred in 2 patients while they were receiving deep x-ray therapy; in both death occurred before completion of treatment.

Death from gastrointestinal causes occurred in 13 per cent of our series. This was due principally to intestinal obstruction. The obstruction in all cases was due to direct invasion and involvement of the large bowel by the neoplasm; in no instance was the obstruction due to adynamic causes. Invasion was further exemplified by the occurrence of perforation of the bowel due to spreading carcinoma with resultant generalized peritonitis. Since generalized abdominal carcinomatosis is a relatively infrequent finding in patients with carcinoma of the cervix, intestinal obstruction was usually due to regional pelvic involvement. Most of the bowel obstruction occurred in the region of the rectum and rectosigmoid. This was produced as a result of the spread of the carcinoma out through the leaves of the broad ligament directly to the bowel or from massive carcinomatous involvement of and extension to the retroperitoneal lymph nodes which secondarily compromised the lumen. In one patient treated with radium to the extent of 5,520 milligram hours over a 24-hour period, a noncarcinomatous large bowel obstruction was found.

Peritonitis was responsible for five deaths, or 9 per cent of the entire group of patients. Peritonitis, we feel, occurred in these patients as a direct result of spread of infected and necrotizing carcinoma from the primary site out into the pelvic peritoneum with perforation at that point, as well as by bowel perforation by spreading neoplasm. Spontaneous abdominal ureterostomy occurred as the result of direct invasion and perforation of the ureter by carcinoma in one patient; peritonitis however was the immediate cause of death in this patient.

In only one patient was hemorrhage the immediate cause for death. This patient had been bleeding rather briskly for several months without transfusion and shortly after admittance to our hospital died from a terminal overwhelming hemorrhage as the result of erosion of large vessels by the carcinoma. While hemorrhage is considered to be a common cause of death in patients with cervix carcinoma, this was not true in our series.

It is interesting to note that the patient with primary gall-bladder carcinoma died as the result of that carcinoma and its metastases. At the time of autopsy there was no remnant of the cervical neoplasm discernible.

A study was also made to determine the spread of cervix cancer. The route of spread from the primary is not selective, hence any structure along this route may be involved if and when the extension process becomes massive enough.

The genitourinary system was the most commonly affected, and the lymphatic system second. The retroperitoneal nodes were the most frequently involved in the lymphatic system. It was found that, in many of the cases where no actual neoplastic involvement of organs could be shown, damage nonetheless

TABLE V. SITES OF METASTASES.

| | | |
|------------------------|---|----|
| Urinary tract | Bladder | 25 |
| | Ureter | 24 |
| Gastrointestinal tract | Rectum | 16 |
| | Colon | 8 |
| Lymphatic system | Retroperitoneal nodes | 23 |
| | Iliac nodes | 5 |
| | Peribronchial nodes | 4 |
| | Supraclavicular nodes | 1 |
| | Inguinal nodes | 1 |
| Bone | Rib | 3 |
| | Pubis | 1 |
| | Knee | 1 |
| | Lumbar spine | 2 |
| | Femur | 1 |
| | Cervical spine | 1 |
| Parenchymatous organs | Liver | 6 |
| | Heart Muscle | 2 |
| | Lungs | 11 |
| | Kidney | 1 |
| | Spleen | 1 |
| Serous cavities | Generalized abdominal Carcinomatosis | 5 |
| | Pelvic peritoneum | 10 |
| | Pleura | 2 |
| Muscle | Pectoralis major muscle | 3 |
| | Diaphragm | 1 |
| | Psoas muscle | 1 |
| Miscellaneous | Sacral plexus | 2 |
| | Iliac artery | 3 |
| | Mesenteric vein (Ca. thrombus) | 1 |
| | Breast | 1 |
| | Bone marrow | 1 |
| None | | 10 |

occurred due to involvement of nodes surrounding the organ. In this way indirect involvement of these structures was effected by the spread and growth of metastatic carcinoma in the nodes. The lower urinary tract was the most frequently involved local site of spread, while the most common site for remote spread was the lung. In the organs involved by constriction, we have found that reduction in size of the lumina has been due not only to invasive malignancy into the structure itself but also to the growth of neoplasm in the immediately surrounding area. This is particularly true in ureteral and large bowel obstruction.

In spreading from the cervix, carcinoma progresses through the lymphatic tributaries which drain the pelvic organs back into the general lymphatic circulation and attack or involve any organ in its path of spread. It is due to involvement and invasion in, as well as growth in these paths of spread, that patients die as the result of carcinoma of the cervix and not from the local primary neoplasm, except in the rare case of hemorrhage. Therefore, radium and x-ray therapy in cervix cancer should be directed toward controlling not only the local site, but also to the sites to which the neoplasm will first spread. Gynecologists and roentgenologists today are not concerned alone with the destruction of the primary site but also seek to prevent its spread and invasion. For this reason clinical examination of all patients with carcinoma of the cervix should include a complete physical examination, pelvic examination, rectal and urologic examination. Satisfactory evidence of extension beyond the cervix cannot be elicited without rectal examination. These clinical procedures should be supplemented by routine x-ray study of the chest and bony structures whenever indicated.

Summary

The causes of death in 55 patients dying with carcinoma of the cervix have been reviewed and analyzed.

Ureteral obstruction (40 per cent), pulmonary causes (31 per cent), and gastro-intestinal causes (13 per cent), account for the majority of deaths among patients with cervix carcinoma.

Nephrostomy, cutaneous ureterostomy, palliative colostomy, and shunting bowel anastomoses may not only lengthen life but may also be lifesaving measures. While nephrostomy and ureterostomy have not yet reached perfection, their continued and more frequent use may lead to improved technic.

Every positive therapeutic measure to control these causes of death must be instituted early to further lower a mortality rate that has already been significantly reduced.

520 MAYER BUILDING.

IS TOXEMIA OF PREGNANCY AN ALLERGIC REACTION?

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THE cause of toxemia of pregnancy presents a great challenge to medical research. Uremia, bacteria, toxins, faulty metabolism, and endocrine imbalance have all been blamed. In spite of the tremendous amount of work that has already been put into it, the real etiology is still unknown.

The toxemic manifestations occur only during pregnancy and often disappear soon after delivery or upon death of the fetus. This sequence suggests that the cause may be connected with the product of conception. The fetus has been eliminated as the cause of the trouble, since these manifestations also occur in molar pregnancy. Therefore, the placenta itself has for a long time been looked upon as the source of all the troubles.

The placental aspects have been attacked from all angles. Those workers who advocated hormonal imbalance have reported divergent findings. Smith and Smith¹⁻³ reported high gonadotrophic and low estrogenic levels in toxemic patients. Their theory was substantiated by Anselmino,⁴ Rakoff,⁵ and White and co-workers,⁶ who discovered excessive gonadotropin in the body fluid of these patients. Taylor and Seadron,⁷ however, did not find any significant difference in the hormonal values between normal and toxemic patients. Others found acetylcholine in the placenta and identified it as a potent vasodilator. Hofbauer¹⁶ then put forth the theory that acetylcholine held the delicate balance between the blood pressure stimulating and depressing principles.

Recent interest in antigen-antibody reaction in diseases has been intensified by the work done with anti-kidney serum of Masugi^{8, 9} and Smadel.¹⁰⁻¹² Dobrowski¹³ reported that placenta antiserum interrupted pregnancy in guinea pigs and rabbits. Seegal and Loeb¹⁴ also encountered the same experience in rats injected with rabbit antiplacenta serum.

It is a common finding of the obstetricians that repeated pregnancies intensify all the symptoms and signs of toxemia of pregnancy. The present experiment was undertaken to find out whether toxemia of pregnancy in rats can be produced by antigen-antibody reaction. A group of virgin albino rats were sensitized by frequent intraperitoneal injections of placental suspension. After a sufficient length of time was allowed for the antibodies to develop, these immunized rats were then allowed to become pregnant. During their periods of gestation, they were tested very carefully for any manifestations of toxemia.

Materials and Methods

Preparation of placental suspensions.—Twenty albino female rats were allowed to become pregnant at fixed intervals so that they could furnish the

group. Significance of the difference between the highest (over 85 Gm. per day) and lowest (under 55 Gm. per day) protein groups is indicated only where significant at the 0.05 level of probability or better; other differences have been tested, but are not significant by this criteria. Longitudinal growth curves of weight and length for the sixty most extreme complete cases are shown in Fig. 1. All weights, lengths, and numbers of ossification centers are expressed as T-scores.

Weight (see Table I).—At birth and one month, excluding premature infants, there are no progressive decreases in mean weights with decreasing protein intake as would be expected if a high degree of association existed between these factors. When premature infants are included, there is a suggestive relationship at both birth and one month. Examination of our data revealed that this greater association is due to the addition of a single very extreme case, protein = 26 Gm. per day, weight = -2.2σ at birth and -2.9σ at one month. (This case is not included at six or twelve months.) None of the correlations are significant at these two ages, nor is there a significant difference between the means for the highest and lowest protein groups.

TABLE I. WEIGHT (T-SCORES; MALE AND FEMALE)

| <i>Birth:</i> | Protein, Gm./Day | Excluding Premature | | | Including Premature | | |
|-----------------------|------------------|--|-----|--------------|--|-----|--------------|
| | | N | M | $\pm \sigma$ | N | M | $\pm \sigma$ |
| | 85 or more | 19 | 54 | 10 | 20 | 53 | 12 |
| | 70 to 84 | 81 | 51 | 7 | 83 | 50 | 8 |
| | 55 to 69 | 74 | 51 | 10 | 76 | 51 | 10 |
| | 45 to 54 | 19 | 52 | 7 | 19 | 52 | 7 |
| | under 45 | 3 | 56 | - | 5 | 49 | 9 |
| | under 55 | 22 | 52 | 7 | 24 | 51 | 8 |
| | Correlation: | $r = +0.04$ (N = 196) (not significant) | | | $r = +0.06$ (N = 203) (not significant) | | |
| <i>One Month:</i> | Protein, Gm./Day | Excluding Premature | | | Including Premature | | |
| | | N | M | $\pm \sigma$ | N | M | $\pm \sigma$ |
| | 85 or more | 16 | 54 | 10 | 16 | 54 | 10 |
| | 70 to 84 | 70 | 51 | 8 | 71 | 50 | 9 |
| | 55 to 69 | 66 | 49 | 9 | 67 | 49 | 9 |
| | 45 to 54 | 16 | 52 | 6 | 16 | 52 | 6 |
| | under 45 | 3 | 57 | - | 5 | 45 | 17 |
| | under 55 | 19 | 52 | 7 | 21 | 50 | 10 |
| | Correlation: | $r = +0.06$ (N = 171) (not significant) | | | $r = +0.16$ (N = 175) (not significant) | | |
| <i>Six Months:</i> | Protein, Gm./Day | Excluding Premature | | | Including Premature | | |
| | | N | M | $\pm \sigma$ | N | M | $\pm \sigma$ |
| | 85 or more | 17 | 54 | 10 | 17 | 54 | 10 |
| | 70 to 84 | 68 | 51 | 10 | 70 | 51 | 10 |
| | 55 to 69 | 66 | 51 | 9 | 68 | 51 | 9 |
| | 45 to 54 | 17 | 51 | 9 | 17 | 51 | 9 |
| | under 45 | 3 | 51 | - | 4 | 48 | - |
| | under 55 | 20 | 51 | 9 | 21 | 50 | 9 |
| | Correlation: | $r = +0.10$ (N = 171) (not significant) | | | $r = +0.12$ (N = 176) (not significant) | | |
| <i>Twelve Months:</i> | Protein, Gm./Day | Excluding Premature | | | Including Premature | | |
| | | N | M | $\pm \sigma$ | N | M | $\pm \sigma$ |
| | 85 or more | 17 | 54* | 9 | 17 | 54* | 9 |
| | 70 to 84 | 67 | 51 | 11 | 69 | 51 | 12 |
| | 55 to 69 | 65 | 49 | 10 | 67 | 50 | 10 |
| | 45 to 54 | 17 | 48 | 11 | 17 | 48 | 11 |
| | under 45 | 2 | 42 | - | 3 | 41 | - |
| | under 55 | 19 | 47* | 11 | 20 | 47* | 11 |
| | Correlation: | $r = +0.21$ (N = 168) P = 0.05 | | | $r = +0.22$ (N = 173) P = 0.05 | | |

*Difference between highest (85 or more) and lowest (under 55) protein groups is significant at the 0.05 level of probability.

given in another paper.¹¹ Quantitative values for average daily intakes of protein in grams are the basis for this present study.

Anthropometric measurements including crown-heel length are taken on the newborn infants at home or at the hospital by members of the Fels staff, usually within twenty-four hours of birth. A physical examination is made by the Fels pediatrician at this time. Whenever possible complete skeletal x-rays are taken by the hospital staff for us. Subsequently, infants are brought to Fels at one, six, and twelve months for physical examination, anthropometric measurements, and x-rays. Measurements of the children used in this study are: weight in kilograms, crown-heel length in centimeters, and number of ossification centers present.¹² The illness histories, physical examinations, and infant nutrition records obtained during these visits will be considered in a later paper.

All cases of hyperthyroidism, toxemias of pregnancy, multiple births, erythroblastosis fetalis, and other interfering illnesses were omitted from this study. Tables show birth weights, lengths, etc., of the group when prematures are excluded, and also when they are included in the group. Prematurity as used in this study is defined as a child of less than eight months menstrual age.

The mothers' weights used are the weights at the last menstrual period prior to pregnancy.

Method

The mothers were divided into five groups according to their average daily intake of protein: 85 Gm. or more, 70 to 85 Gm., 55 to 70 Gm., 45 to 55 Gm., and under 45 Gm. per day. These particular groupings were chosen to correspond to those used by Burke and associates, so that results of the two studies may be easily compared.

Mean birth weights and birth lengths of the infants were calculated for each protein group. Significance of the difference between the means for the highest (over 85 Gm. per day) and lowest (under 55 Gm. per day) protein groups was tested. This same procedure was applied to weight and length at one, six, and twelve months of age. The number of ossification centers for each protein group at each age was similarly studied.

Pearson coefficients of correlation (r) between the mothers' prenatal protein intake and the weight, length, and ossification of the infants were calculated for each age. All correlations were computed both excluding and including premature infants. Significance of each correlation was tested.

Growth patterns could not be adequately studied using the entire group of infants, since there are a number of incomplete cases in each protein group. An extreme case with data missing at one or more age levels would distort the growth curve. To adequately study growth changes with age, a longitudinal study was made using the thirty highest and thirty lowest cases (half male, half female) with *complete* data on length and weight. Significance of the differences between the means of the highest and lowest cases was tested, as were the differences in status for each group between birth and twelve months. It should be remembered that the reliability of growth curves is greatly increased by the use of longitudinal data.

The use of T-scores makes it possible to combine the sexes, quite as Burke and his co-workers combined them by using percentiles. A T-score is derived by adding 50 to ten times the standard deviation (sigma deviation) from the mean for any given characteristic.

Results

The means (m) and sigmas (σ) of weight, length, and ossification for each protein group are presented in Tables I, II, and III. The coefficients of correlation (r), together with their significance, are given directly below each age

As with weight, the greatest degree of relationship between the prenatal protein intake and the length of the infants is present at twelve months. There is a definite, progressive decrease in means with decreasing protein, both excluding and including premature infants, with a significant ($P = 0.05$) difference between the lengths of the protein groups over 85 Gm. per day and under 55 Gm. per day. Both correlations at twelve months are significant at the 0.05 level of probability.

Ossification (see Table III).—At birth there is a suggestive, though not statistically significant, *inverse* association between the protein intake of the mother and the number of ossification centers present. With each decrease in protein there is an increase in the number of centers present. The differences between the extreme groups are not significant, nor are the correlations.

TABLE III. OSSIFICATION (T-SCORES; MALE AND FEMALE)

| Birth: | Protein, Gm./Day | Excluding Premature | | | | Including Premature | | | |
|----------------|------------------|---------------------------|----|-------|----------|---------------------------|----|-------|----------|
| | | N | M | \pm | σ | N | M | \pm | σ |
| | 85 or more | 7 | 47 | | 8 | 7 | 47 | | 8 |
| | 70 to 84 | 22 | 50 | | 10 | 22 | 50 | | 10 |
| | 55 to 69 | 31 | 51 | | 7 | 32 | 51 | | 7 |
| | 45 to 54 | 11 | 53 | | 14 | 11 | 53 | | 14 |
| | under 45 | 1 | 63 | | - | 2 | 58 | | - |
| | under 55 | 12 | 54 | | 13 | 13 | 54 | | 13 |
| | Correlation: | $r = -0.21$ ($N = 72$) | | | | $r = -0.20$ ($N = 74$) | | | |
| | | (not significant) | | | | (not significant) | | | |
| One Month: | Protein, Gm./Day | Excluding Premature | | | | Including Premature | | | |
| | | N | M | \pm | σ | N | M | \pm | σ |
| | 85 or more | 14 | 54 | | 13 | 14 | 54 | | 13 |
| | 70 to 84 | 57 | 49 | | 9 | 58 | 49 | | 9 |
| | 55 to 69 | 59 | 49 | | 10 | 60 | 49 | | 10 |
| | 45 to 54 | 16 | 52 | | 13 | 16 | 52 | | 13 |
| | under 45 | 3 | 60 | | - | 4 | 59 | | - |
| | under 55 | 19 | 53 | | 13 | 20 | 53 | | 13 |
| | Correlation: | $r = -0.05$ ($N = 149$) | | | | $r = -0.06$ ($N = 152$) | | | |
| | | (not significant) | | | | (not significant) | | | |
| Six Months: | Protein, Gm./Day | Excluding Premature | | | | Including Premature | | | |
| | | N | M | \pm | σ | N | M | \pm | σ |
| | 85 or more | 15 | 55 | | 11 | 15 | 55 | | 11 |
| | 70 to 84 | 64 | 50 | | 7 | 66 | 50 | | 7 |
| | 55 to 69 | 59 | 50 | | 6 | 61 | 49 | | 6 |
| | 45 to 54 | 16 | 54 | | 12 | 16 | 54 | | 12 |
| | under 45 | 3 | 61 | | - | 4 | 59 | | - |
| | under 55 | 19 | 52 | | 12 | 20 | 55 | | 12 |
| | Correlation: | $r = -0.04$ ($N = 157$) | | | | $r = -0.04$ ($N = 162$) | | | |
| | | (not significant) | | | | (not significant) | | | |
| Twelve Months: | Protein, Gm./Day | Excluding Premature | | | | Including Premature | | | |
| | | N | M | \pm | σ | N | M | \pm | σ |
| | 85 or more | 15 | 56 | | 10 | 15 | 56 | | 10 |
| | 70 to 84 | 62 | 49 | | 9 | 64 | 49 | | 9 |
| | 55 to 69 | 59 | 48 | | 7 | 61 | 48 | | 7 |
| | 45 to 54 | 16 | 52 | | 16 | 16 | 52 | | 16 |
| | under 45 | 2 | 55 | | - | 3 | 54 | | - |
| | under 55 | 18 | 53 | | 15 | 19 | 53 | | 15 |
| | Correlation: | $r = +0.03$ ($N = 154$) | | | | $r = +0.03$ ($N = 159$) | | | |
| | | (not significant) | | | | (not significant) | | | |

No significant relationship is shown at one, six, or twelve months. There is, however, a peculiar, consistent pattern shown at each of these ages. The greatest number of centers is present in the extreme protein groups, those over 85 and those under 55 Gm. per day. The in-between groups (between 55 and 85) show the fewest number of centers at all three age levels. Certainly differences in maternal protein intake are not manifested in retarded skeletal growth of the infants in this group.

At six months there is again a suggestive slight decrease in mean weights with decreasing protein. The differences between the highest and lowest groups are not significant, nor are the correlations.

A significant association between protein intake and weight of the infant is shown only at twelve months. There is a definite, progressive decrease in mean weights with decreasing protein, and a difference significant at the 0.05 level of probability between the extreme protein groups. The coefficients of correlation are also significant at the 0.05 level of probability.

Length (see Table II).—Length shows a very similar pattern of association with prenatal protein intake to that shown by weight. At birth and one month there is little apparent association until the premature infants are included. Here, as with the weights, the addition of the same extreme case (protein = 26 grams; length = -3.5σ at birth, -4.0σ at one month) creates a slight progressive decrease in mean length with decreasing protein intake. The differences between the highest and lowest groups are not statistically significant, nor are the correlation coefficients.

There is no significant association shown with length at six months.

TABLE II. LENGTH (T-SCORES; MALE AND FEMALE)

| Birth: | Protein, Gm./Day | Excluding Premature | | | Including Premature | | |
|----------------|------------------|--|-----|--------------|--|-----|--------------|
| | | N | M | $\pm \sigma$ | N | M | $\pm \sigma$ |
| | 85 or more | 11 | 55 | 13 | 12 | 54 | 13 |
| | 70 to 84 | 44 | 52 | 7 | 44 | 52 | 7 |
| | 55 to 69 | 52 | 50 | 8 | 53 | 50 | 8 |
| | 45 to 54 | 14 | 50 | 9 | 14 | 50 | 9 |
| | under 45 | 2 | 55 | - | 4 | 42 | - |
| | under 55 | 16 | 51 | 9 | 18 | 49 | 12 |
| | Correlation: | $r = +0.13$ (N = 123) (not significant) | | | $r = +0.17$ (N = 127) (not significant) | | |
| One Month: | Protein, Gm./Day | Excluding Premature | | | Including Premature | | |
| | | N | M | $\pm \sigma$ | N | M | $\pm \sigma$ |
| | 85 or more | 14 | 54 | 10 | 14 | 54 | 10 |
| | 70 to 84 | 61 | 52 | 10 | 62 | 52 | 10 |
| | 55 to 69 | 59 | 49 | 11 | 60 | 49 | 11 |
| | 45 to 54 | 16 | 51 | 10 | 16 | 51 | 10 |
| | under 45 | 3 | 60 | - | 5 | 46 | 20 |
| | under 55 | 19 | 52 | 10 | 21 | 50 | 14 |
| | Correlation: | $r = +0.09$ (N = 153) (not significant) | | | $r = +0.16$ (N = 157) (not significant) | | |
| Six Months: | Protein, Gm./Day | Excluding Premature | | | Including Premature | | |
| | | N | M | $\pm \sigma$ | N | M | $\pm \sigma$ |
| | 85 or more | 16 | 52 | 7 | 16 | 52 | 7 |
| | 70 to 84 | 68 | 50 | 9 | 70 | 50 | 10 |
| | 55 to 69 | 62 | 48 | 9 | 64 | 47 | 10 |
| | 45 to 54 | 17 | 48 | 10 | 17 | 48 | 10 |
| | under 45 | 3 | 55 | - | 4 | 53 | - |
| | under 55 | 20 | 49 | 9 | 21 | 49 | 9 |
| | Correlation: | $r = +0.12$ (N = 166) (not significant) | | | $r = +0.11$ (N = 171) (not significant) | | |
| Twelve Months: | Protein, Gm./Day | Excluding Premature | | | Including Premature | | |
| | | N | M | $\pm \sigma$ | N | M | $\pm \sigma$ |
| | 85 or more | 16 | 53* | 8 | 16 | 53* | 8 |
| | 70 to 84 | 64 | 51 | 10 | 66 | 51 | 11 |
| | 55 to 69 | 64 | 48 | 10 | 66 | 48 | 10 |
| | 45 to 54 | 16 | 47 | 9 | 16 | 47 | 9 |
| | under 45 | 2 | 47 | - | 3 | 48 | - |
| | under 55 | 18 | 47* | 9 | 19 | 47* | 9 |
| | Correlation: | $r = +0.22$ (N = 162) $P = 0.05$ | | | $r = +0.17$ (N = 167) (not significant) | | |

*Difference between the highest (85 or more) and lowest (under 55) protein groups is significant at the 0.05 level of probability.

Discussion

Weight.—While correlation coefficients between infant weight and maternal protein intake values are on the positive side at each age level, it is only at twelve months that these coefficients become statistically significant. The fact that the three coefficients, none of which is statistically significant, are all on the positive side is mildly suggestive of a positive though slight relationship.

Length.—Only one of the correlation coefficients between infant's length and mother's protein intake values is at a significant level, and that barely so. Again, however, all of the coefficients are positive, a fact which suggests the possibility of some relationship between mother's protein values and length.

Ossification.—There are no statistically significant correlation coefficients between the ossification of the infants during the first year of life and the mother's protein intake. Some of the coefficients are positive and some negative, but all are small.

The rather considerable difference in the results of our study as compared with that of Burke and Stuart is, at first sight, somewhat puzzling. Burke found a correlation coefficient of 0.80 between protein intake and length of the child. She also found a higher relationship between protein intake and the infant's weight. Yet, in our series of cases, approximately the same number of mothers and children were studied, but the relationships we have found are on the borderline of significance and far below those of Burke and associates. There are, perhaps, a number of differences in the study which may account for our differences in result. It is difficult from Burke's description to understand exactly the method she used to arrive at numerical values for the protein intake for the women she studied. In an early publication Burke states "a closer analysis of data obtained by the nutrition history method is unwarranted, and more exact calculation of diets is justified only in the case of weighed samples."⁴ She also states that "the average daily protein content of the diets has been estimated in grams. Table I shows the standards used in rating the protein intake of the mothers."² It is not clear to us whether she assigned a rating of excellent, good, fair, and poor to the various diets, and then on the basis of nutrition standards stated by others assigned a numerical value to the ratings, or whether she estimated directly from her nutrition histories the grams of protein ingested. She apparently did not arrive at her values by a method of calculation of values from food tables—the method we have used. This difference in technique may account for some of the differences in results.

In the Burke studies the calculated daily intake of protein tended to be lower than in our series. For example, 61 of 183 mothers had protein intakes of 54 Gm. per day or under, whereas, in our series, only 24 mothers of a group of 203 have protein diets under 55 grams. Thus, the drain on protein reserves by Burke's mothers probably was greater than in our series, and the effects of inadequate protein diet might be supposed to be greater.

Burke has apparently included in her series several cases of toxemia of pregnancy which were treated, at least in some instances, by being placed upon a very low protein diet. It is well known that infants of toxic mothers tend

Growth Curves (see Fig. 1).—The sixty most extreme cases with complete data at all ages were used for a longitudinal study of the differences and growth changes. The difference between the thirty highest and thirty lowest cases is 29 Gm. of protein, significant at greater than the 0.001 level of probability. In spite of the extreme differences between the groups chosen for comparison, the differences shown in weight and length are not statistically significant or even nearly so (the greatest difference has a probability of 0.4). Except for birth weight where there is no difference, infants in the lowest protein group are somewhat shorter and lighter at all ages. There is a greater difference in lengths than in weights of the two groups. There is no observable age trend for either length or weight, nor any significant difference between various age levels.

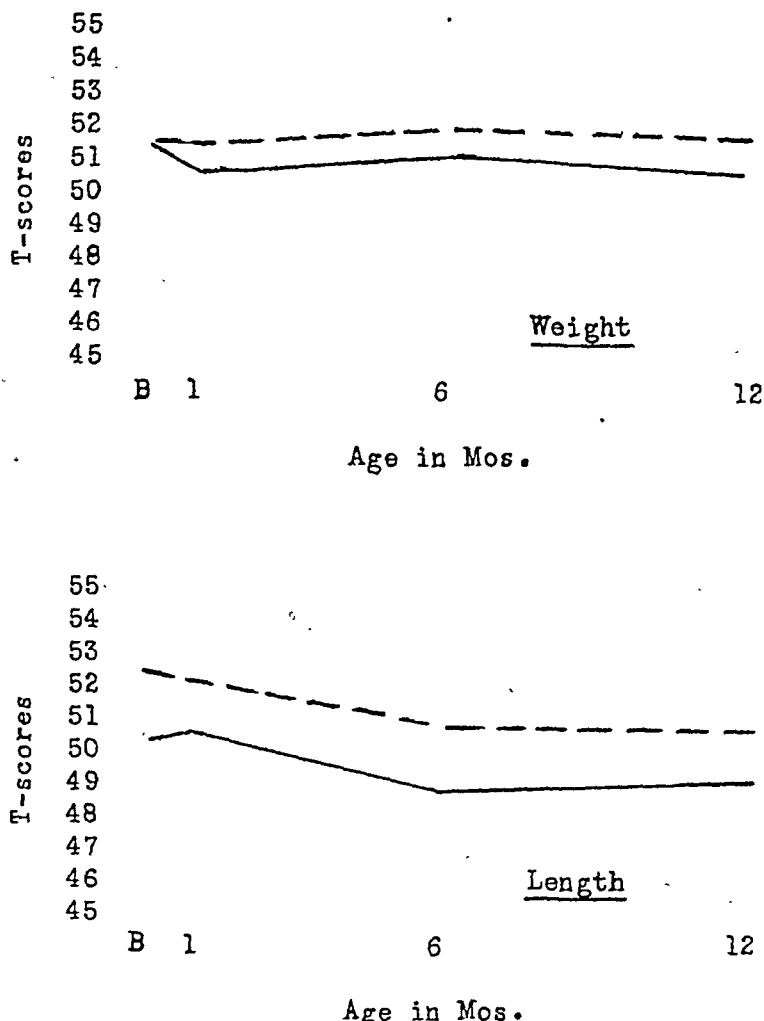


Fig. 1.—Mean growth patterns for 30 highest and 30 lowest complete cases.

— — — — — = Highest protein group, N = 30; mean protein = 58 (T-score).

————— = Lowest protein group, N = 30; mean protein = 38 (T-score).

(No significant difference between high and low groups; no significant age change.)

One might advance the hypothesis that large women, other factors being equal, eat much protein and that large women also have large babies. If so, a false implication of the importance of high protein consumption might emerge. However, the correlation between mother's weight and her calculated protein ingestion is -0.04 . Since there is no apparent relationship between mother's size and her protein ingestion, no spurious effect can be operative in our group.

A PREMATURE SURVIVAL INDEX AND THE CONDUCT OF PREMATURE LABOR

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THERE is today no unanimity as to precisely what constitutes a "premature infant." No standard has been universally accepted. The frequent statistical division of prematures into viable and nonviable, appears to us to be unsound, illogical, and contrary to basic definitions. In the first place, the term "viable premature" is a double positive, for a premature infant, by definition, is one which is viable. It follows then that so-called "nonviable prematures" are, in the strict sense, abortions. We are of the opinion that, for statistical purposes at least, the term *premature* should be reserved for fetuses born at varying periods before they can be expected to survive with the ease shown by those carried nearer to term, and *abortion* for those born before the twenty-eighth week of gestation. Furthermore, the terms premature infant and viable infant are commonly used synonymously. It is acknowledged that many small premature infants, even when delivered alive in good condition, will not survive. Moreover, occasionally a fetus, which, according to all current standards, is an abortion, will survive under appropriate pediatric care. An excellent example of the latter is the fetus reported by Monro¹ to have had a minimum recorded weight of 420 Gm. (0.924 pounds). This, incidentally, is the smallest surviving infant on record.

Various criteria are in use to determine whether a fetus is viable. Thus, on the basis of duration of pregnancy, a fetus which has remained in utero twenty-eight weeks is generally said to be a premature.² The lower limit of prematurity recognized by DeLee³ is twenty-six weeks' gestation. The Catholic church,⁴ too, recognizes a fetus from a twenty-six weeks' gestation as being premature. For obvious reasons, duration of pregnancy in some instances as calculated from onset of the last menstrual period is inaccurate. It must be recalled that many women do not record the dates of their menses and therefore have no precise data on the last menstrual period. Again, the date of ovulation and of conception cannot be dated with precision from the onset of the previous menstrual cycle, but rather from the onset of the next menses, which, of course, does not occur in the event of pregnancy. The inaccuracy from menstrual history becomes even greater in those few women who do not menstruate regularly, and in those few with cycles far above twenty-eight days. Notwithstanding these inherent errors, which careful history taking will constantly reduce, and in view of the fact that the great majority of patients do menstruate roughly every twenty-eight days, the gestational period as calculated from onset of last menses is still a usable factor.

to be very small, not because of low protein intake primarily, but apparently as a result of thrombosis of the placental vessels. The effect of including even a few such infants in the series would be to increase tremendously the correlation between mother's protein intake and size of the infant. Yet, actually, in those instances both protein intake and size of the infant would be dependent upon a third factor—the toxemia.

Summary

In a study of 203 mothers' diet histories and the relationship to the length, weight, and ossification of their infants at birth, one month, six months, and twelve months of age, we have been unable to demonstrate unequivocally a relationship between any of these factors and protein intake of the mothers during pregnancy. There is a suggestion of a relationship between weight and length and protein intake. Our conclusion from this study is not that protein intake has no effect upon the status of the infant at birth or during the first year, but rather that protein intake must fall below the levels current in our groups before such an effect is clearly demonstrable. Our results should not be interpreted as a basis for disregarding the importance to the child of good nutrition during pregnancy.

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typical with premature infants, will measure long, due to undue lengthening at all joints, whereas the vigorous, well-muscled term or postmature newborn will not always relax immediately upon being picked up by the ankles and will thus produce a short measurement. The highest precision can be obtained with an anthropometer after some experience—experience primarily on the part of the assistant who stretches the newborn out at a maximum length on his back on a non- or poorly padded examining table.

The most unreliable standard of viability or prematurity is that attempt by law governing reportable gestations. The Model Vital Statistics Act of 1941 requires that all gestations advanced to the fifth month be reported. Since there is no specification to the contrary, it is assumed that calendar months are meant. Sixteen states and the District of Columbia have other legal limits, varying from Maryland (any recognizable product of conception) to those of the states of Washington and Indiana (seven months or over).

Not infrequently more than one standard is utilized in order to ascertain the presence of prematurity. For example, Dana⁶ defines the premature infant as one whose birth weight is between 1,500 and 2,499 Gm., or whose total length is between 35 and 44.9 cm., regardless of the duration of pregnancy. This combination is fairly commonly employed in teaching institutions. We are aware of none utilizing a combination of more than two, although Hess and Chamberlain⁷ contend that age, length, and weight of the premature infant are the main factors concerned with its viability.

From the foregoing, it appears quite obvious that there are several criteria in use for the diagnosis of prematurity, but that all are variable factors. It has occurred to one of us (H. W. J.) that a combination of a larger number of factors of the small premature infant should produce less inaccuracy in the diagnosis of prematurity and in prognosticating the probable outcome than has thus far been possible with any of these factors used alone. The assumption is that the inaccuracies in single factors will tend to be equalized when combined with each other. Accordingly, we have developed an index for prematurity from a combination of five factors.

Only twenty-three premature infants thus far comprise the series. They are nonselected, but consecutive private cases delivered at St. Joseph's Maternity Hospital over a period of ten months. Stillbirths and those succumbing in the immediate antenatal period are not included.

The factors used to establish the five-point premature survival index are the following: (a) gestational period is calculated from the first day of the last normal menstrual period regardless of regularity or irregularity of the menstrual cycle in each instance. In the current series the cycles varied from twenty-eight to thirty-two days with one exception, in which the cycle was forty-five to sixty days, and nothing is known of the cycles of three other patients. (b) Weight of the newborn was obtained in ounces. (c) The total, or crown-heel, length was obtained in inches in the usual manner, i.e., by measuring with a steel tape along the side of the body suspended at the ankles. (d) Occipitofrontal circumference was recorded in inches. (e) The circumference

Another standard for prematurity, and the one most commonly used, is birth weight or minimum recorded weight, since many premature infants are not weighed at birth, but this function postponed for days, until such time as the premature infant is considered to be in good enough physical condition to be handled or until it expires. The generally accepted weight limits for prematurity are 1,500 Gm. (3.3 pounds) and 2,499 Gm. (5.5 pounds). The lower limit is of particular concern to us. There are a fair number of fetuses of gestations of at least twenty-eight weeks with birth weights below 1,500 Gm., even some below 1,000 Gm. (2 pounds 3 ounces). This occurrence is frequent enough to have prompted Haas⁵ to suggest 1,000 Gm. as the lower weight limit of prematurity. Naturally, those premature infants with birth weights below 1,000 Gm. have a very poor expectancy for life, yet it is interesting to record that a recent survey of the literature⁵ reveals that there are at least 54 such cases on record. Comment on the smallest of these has already been made. With the above facts in mind, it becomes quite obvious that birth weight is indeed a very poor criterion of prematurity. We must remember that birth weight of the newborn is an index of the weight of its ancestors, and, since there are very wide ranges in weights of adults, there will, accordingly, be great normal variations in weights of newborn infants, whether they are born prematurely or at or near term. Again, some maternal diseases, notably chronic nephritis, have a very detrimental effect upon fetal nourishment, and frequently cause children to be produced far below the birth weight normally expected for the period of gestation. The ease in rearing these, if born alive in good condition, corresponds to the advanced gestational period and not to the subnormal birth weight. In other words, they do not afford the difficulty found with premature infants of the same weight born of non-nephritic mothers. Three of the above noted 54 raised premature infants with weights of less than 1,000 Gm. were reported by Haas,⁵ and it is an interesting commentary that two of these three were born of nephritic mothers. Occasionally one finds very marked differences in birth weight of a pair of identical twins. An outstanding example of this was noted by one of us (A. L. D.) when single-ovum twins were delivered at thirty-three weeks' gestation with one weighing 1,005 Gm. and the other 2,260 Gm. The smaller was raised with very little more difficulty than the larger.

Still another standard for determination of prematurity is body length. Crown-heel length or standing height is commonly used. The generally accepted limits of this criterion for prematurity in most teaching institutions are at least 35 cm., but less than 45 cm. total length. When we realize that body length is an hereditary factor, it is immediately apparent that this standard is reliable only in children born of parents of average height. Anyone who has measured the length of many newborns, and especially he who has remeasured some by the same or by various methods, will recognize certain inherent difficulties with the precise determination of this diameter of a newborn. The commonest method of mensuration here is to suspend the newborn from the ankles while measuring along the side of the body with a tape. A washable tape is, of course, not precise. The newborn with decreased muscle tone, as is

placentas according to schedule. The date of copulation was timed by daily vaginal smears. Cesarean sections were performed on these rats one day before term. The placentas were removed aseptically and carefully washed free of blood and ground into small pieces in a glazed porcelain mortar and made up to a 20 per cent suspension with saline solution. Each suspension was used the day it was prepared, as described in the following paragraph.

Preparation of experimental animals.—Ten mature female albino rats weighing 250 to 300 Gm. were kept on Purina dog chow with weekly supplements of yeast, cod liver oil, and hamburger. These rats were obtained from Rockland Farms. These ten rats were given 2 c.c. of the placental suspension intraperitoneally twice a week for five weeks.

These animals were then allowed to have a rest period of five months. At the end of this time they were mated. From their daily vaginal smears their pregnancies were also closely dated.

Lines of investigations.—Evidence of abnormal toxemic pregnancies was determined by careful observation in the urine, blood pressure, and tissue biopsies.

One week after copulation each of these animals was put into a metabolism cage where daily 17-hour specimens of urine were collected. Each specimen was diluted to 50 c.c. with distilled water, and filtered. 0.5 c.c. of this was added to 9.5 c.c. of sulfosalicylic acid. The albumin content was measured by a Klett colorimeter.

The blood pressure readings were taken twice a week from the tail by Grollman's apparatus. The rats were also carefully watched for edema and any other abnormal manifestations during their pregnancies. Biopsies were taken from different organs for microscopic sections.

TABLE I. ALBUMINURIA IN MG. PER TWENTY-FOUR HOURS

| RAT NO. | DAYS OF PREGNANCY | | | | | | | | | | | | | | | | | | | | DAYS POST PARTUM | | | |
|------------|-------------------|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|---|---|---------------------|--|--|--|
| | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 1 | 2 | 3 | 4 | | | | |
| 1 | 17 | 25 | 22 | 17 | 25 | 27 | 24 | 95 | 49 | 39 | 48 | 33 | 44 | 53 | 55 | 52 | 7 | 0 | 0 | 0 | | | | |
| 2 | 22 | 0 | 32 | 45 | 23 | 40 | 26 | 45 | 49 | 56 | 40 | 37 | 47 | 42 | 49 | 59 | 14 | 12 | 4 | 0 | | | | |
| 3 | 39 | 59 | 72 | 7 | 10 | 27 | 29 | 53 | 45 | 43 | 24 | 39 | 29 | 39 | 59 | 72 | 7 | 0 | 0 | 0 | | | | |
| 4 | 19 | 22 | 22 | 20 | 20 | 20 | 55 | 50 | 36 | 21 | 36 | 23 | 39 | 59 | 52 | 60 | 12 | 0 | 0 | 0 | | | | |
| 6 | 22 | 22 | 26 | 41 | 27 | 29 | 59 | 56 | 58 | 32 | 29 | 32 | 34 | 52 | 27 | 59 | 12 | 13 | 0 | 0 | | | | |
| 7 | 13 | 22 | 25 | 25 | 19 | 25 | 14 | 61 | 35 | 38 | 27 | 26 | 45 | 40 | 36 | 47 | 9 | 5 | 5 | 0 | | | | |
| 8 | 20 | 0 | 24 | 27 | 20 | 25 | 27 | 51 | 50 | 36 | 44 | 36 | 40 | 44 | 51 | 59 | 5 | 5 | 0 | 0 | | | | |
| 10 | 49 | 55 | 51 | 27 | 24 | 33 | 30 | 15 | 27 | 20 | 50 | 30 | 39 | 40 | 34 | 34 | 13 | 0 | 0 | 0 | | | | |

Results.—A definite albuminuria developed which, though not heavy, was significant. The urine specimens of this group of animals were frequently tested during the five months prior to their pregnancies, and all during that period were protein free. Furthermore, the albuminuria disappeared quite rapidly during postpartum observation.

Blood pressure studies.—To obtain an accurate reading the rats were heated in an electric cradle to obtain a general hyperemia. The tail was then inserted into a mercury and water cuff. The blood was squeezed away from the tail with the mercury manometer pressure, and the first return of the pulse was registered by the rise of the water manometer as the returning volume of the blood filled the tail.

The normal blood pressure of this group of rats was between 110 to 130 mm. of mercury. As can be seen by the above chart, their blood pressure was definitely raised.

of the chest was obtained at the level of the xiphisternal joint and recorded in inches. Some few infants were weighed immediately after delivery, but all were measured and weighed within twelve hours of birth. Each newborn infant was promptly placed in a preheated incubator in the delivery room, transported to the premature nursery in this incubator, in which it remained under the competent supervision of the pediatric staff. We are not presenting the details of premature infant care supplied this group of newborn infants. Suffice it to say that the premature nursery at St. Joseph's Maternity Hospital is staffed by a group of pediatricians and nurses who have reduced the uncorrected premature infant mortality rate from 45 per cent to 22 per cent since instituting the present régime in an isolated unit of the hospital. Tyson⁸ reports similar reduction in this rate at the Philadelphia Lying-In Hospital with a rate of 56 per cent in 1931 and 26 per cent in 1941.

The index was obtained by adding gestation in weeks, weight in ounces, crown-heel length in inches, head circumference in inches, and chest circumference in inches, and then dividing the total by five. This resulted in indexes ranging from 19.2 to 25.7 for the twenty-three infants. The important data for each is recorded in Table I. Length of labor is not included in the table, but is of considerable importance in as much as precipitate labor is definitely detrimental to any fetus and may be the specific cause of stillborn or neonatal death in premature labors. In this series, there were five precipitate labors, i.e., total labors lasting three hours or less (Cases 3, 6, 8, 16, and 20). The longest total labor was seventeen hours (Case 13). Excluding the three cesarean sections, all of which were done electively, the average labor lasted 7.2 hours. The three mothers delivered by cesarean section were given as anesthetic agents: spinal novocain, local novocain, and cyclopropane, respectively. The remaining twenty which were delivered vaginally received: no anesthesia (four), pudendal block (two), cyclopropane (nine), cyclopropane and ether (one), ether (two), and cyclopropane with nitrous oxide (two). The analgesic drugs used in these labors are too numerous to record. It is, however, worthy of mention that ten received no analgesia in labor, and eight more who received none within three hours of delivery. Two women in premature labor received demeral (100 mg.) and hyosine ($\frac{1}{150}$ grain) hypodermically within one hour of delivery. Another was given pantopon ($\frac{1}{3}$ grain) hypodermically twenty minutes before delivery, and the remaining two received nembutal ($1\frac{1}{2}$ grains) orally one and two hours, respectively, before delivery.

Eleven of these twenty-three premature labors were cared for by physicians in general practice, two by nonboard specialists in obstetrics, and the remaining ten by diplomates of the American Board of Obstetrics and Gynecology, three cases being the largest number cared for by any one physician. Fifteen of the mothers were multiparas, one having had eight previous term pregnancies. The past obstetric history on one is not known, and two were essential primiparas, i.e., had had one or more previous abortions. The remaining five were primigravidas, one of these an elderly primipara. The age range of the mothers coincided with the usual variations on an obstetric service, the youngest being 19 years of age and oldest 41 years, both primigravidas.

TABLE I. DATA ON 23 PREMATURES FOR PREMATURE SURVIVAL INDEX

| CASE NO. | WEEKS GESTATION | WEIGHT (OUNCES) | CROWN-HEEL LENGTH (INCHES) | HEAD (INCHES) | CHEST (INCHES) | INDEX | TYPE OF DELIVERY | TIME LIVED | AUTOPSY |
|----------|--------------------|--------------------|----------------------------------|------------------|-------------------|-------|---------------------------------|------------|---------------------------------|
| 1* | 32½ | 40 | 15 | 10 | 9 | 21.3 | Cesarean section | 2 days | None |
| 2 | 32½ | 57 | 15.6 | 11.8 | 10.2 | 25.6 | High forceps | Living | ---- |
| 3 | 28½ | 35.5 | 14.4 | 10 | 8.4 | 19.4 | Breech extraction | Living | ---- |
| 4 | 29½ | 51 | 16 | 10.5 | 9.5 | 23.3 | Spontaneous | Living | ---- |
| 5 | 29½ | 60.5 | 16.5 | 11.5 | 10.5 | 25.7 | Spontaneous Episiotomy | Living | ---- |
| 6 | 28 | 36 | 15 | 10.2 | 11 | 20.4 | Low forceps Episiotomy | Living | ---- |
| 7* | 28½ | 39 | 16.2 | 10.2 | 8.75 | 20.5 | Spontaneous | 6 hours | None |
| 8 | 29½ | 43 | 16 | 10.5 | 9.5 | 21.7 | Spontaneous | Living | ---- |
| 9 | 29½ | 49 | 15.5 | 11 | 10.5 | 23.1 | Spontaneous | Living | ---- |
| 10 | 28 | 41 | 15 | 10.5 | 9 | 20.7 | Spontaneous | 11 hours | None |
| 11 | 27 | 35.5 | 14.8 | 10 | 8.75 | 19.2 | Spontaneous | 39 hours | None |
| 12* | 30½ | 43 | 15.5 | 10.2 | 9.5 | 21.7 | Spontaneous | 6 days | None |
| 13 | 30½ | 48 | 17 | 11 | 9.75 | 23.3 | Breech extraction Episiotomy | Living | ---- |
| 14 | 28 | 42 | 15.5 | 10.5 | 9.2 | 21.0 | Spontaneous | Living | ---- |
| 15 | 28½ | 36 | 15.25 | 10 | 9 | 19.8 | Low forceps Episiotomy | Living | ---- |
| 16 | 32½ | 52.5 | 16.5 | 11.5 | 10.2 | 24.6 | Spontaneous Episiotomy | Living | ---- |
| 17* | 29½ | 36 | 15 | 10.75 | 8 | 19.9 | Cesarean section | 20 hours | None |
| 18* | 31½ | 40 | 15.25 | 10.8 | 8.7 | 21.2 | Breech extraction | 25 hours | Atelectasis |
| 19* | 30½ | 55 | 16.5 | 11.5 | 9 | 24.5 | Spontaneous Episiotomy | 16 hours | Torn falx and ten- torium |
| 20 | 32½ | 38 | 14.25 | 10 | 9 | 20.7 | Spontaneous | Living | ---- |
| 21 | 32 | 39 | 16.25 | 10.75 | 9 | 21.4 | Cesarean section | Living | ---- |
| 22 | 28 | 41 | 15.25 | 10.25 | 9.5 | 20.8 | Spontaneous | 4½ hours | None |
| 23 | 27 | 40 | 16.25 | 10.5 | 8.5 | 20.5 | Breech extraction | 4 hours | Prematurity |

*Not included in final analysis—see text.

Eight of these twenty-three pregnancies and labors had no known complications. In nine of the remaining fifteen there was premature spontaneous rupture of the membranes. There were only three toxemias of pregnancy, namely, two with severe pre-eclampsia, and the other with pre-eclampsia superadded to arteriosclerosis. Still another presented pyelo-nephritis which she had had in her only other pregnancy and one had a moderately severe hypochromic microcytic anemia, while the twenty-third delivered a badly macerated twin.

For purposes of arriving at a premature survival index, six of the above cases are eliminated from the final analysis since, for various reasons given herewith, the corresponding premature infants were not or are assumed not to have been delivered in good condition.

CASE 1.—A 31½ weeks' gestation delivered by cesarean section under spinal novocain anesthesia at another hospital and transported by automobile to the St. Joseph's Maternity premature nursery.

CASE 7.—A 28½ weeks' gestation from a multigravida (three previous abortions) who had obvious premature separation of the normally implanted placenta. There was no autopsy, but the clinical impression of the cause of neonatal death after six hours was cerebral edema and bilateral atelectasis.

CASE 12.—A 30½ weeks' gestation delivered spontaneously in bed one hour after a hypodermic of demeral and hyosine, and which had partial amputation (?) of two fingers allowing the speculation, in the absence of an autopsy, of the presence of internal anomalies.

CASE 17.—A 29½ weeks' gestation in a primigravida with a long history of infertility and with a diagnosis of severe pre-eclampsia superadded to hypertensive vascular disease, delivered by cesarean section after weeks of palliation. Autopsy revealed only prematurity.

CASE 18.—A 31½ weeks' gestation in a multipara with an apparently normal pregnancy, but delivered by breech extraction under cyclopropane and ether anesthesia. Autopsy showed atelectasis and periportal infiltration.

CASE 19.—A 30½ weeks' gestation in a secundipara whose pregnancy is said to have been normal, and who was delivered spontaneously with episiotomy under cyclopropane anesthesia one hour after demeral-hyosine analgesia. Atelectasis, torn falx cerebri, and tentorium cerebelli, as well as adrenal hemorrhage, were discovered at postmortem examination of this premature.

In Table II, the seventeen premature infants included in the final analysis are listed in ascending order of value of the premature survival index. Three factors of this index, namely, gestational weeks, birth weight, and crown-heel length, are included along with survival of each infant. Obviously, the series is too small to allow deduction of permanent conclusions. However, some few suggestions are worthy of comment. For example, all premature infants with an index of at least 21.0 were raised, whereas only 50 per cent of those with a smaller index survived. The upper bracket includes gestations which are presumed to have been carried for 28 to 33½ weeks, and premature infants with birth weights ranging from 39 ounces (2.4 pounds) to 60.5 ounces (3.8 pounds). Of particular interest in this table is the absence of correlation between gestational period, birth weight, and total length of the infants. An outstanding example of this is seen in Case 5 where the gestational period is said to have been only 29½ weeks, whereas the infant was the heaviest and the longest in the series, these latter two factors helping to produce the largest index. In this connection, it should be pointed out that the mother menstruated regularly every twenty-eight days, and that she first perceived fetal movements at a time which would tend to confirm the accuracy of her menstrual history. In the lower index bracket is found Case 20 which presented the shortest and one of the lightest infants which is believed to have been one of the longest retained in utero in this series.

It is these apparent inconsistencies in one or more of the commonly employed criteria of prematurity which we believe will be overcome by the use of a sizeable number of factors such as offered by our five-point premature survival index. We believe that after further experience we will be able to say that every premature infant born alive in good condition with an index of at least twenty-one should be reared. Very probably experience will show that this figure should be smaller. We hasten to say that we do not consider premature infants below any arbitrarily chosen figure for one or more factors as hopeless cases. No matter how small the liveborn product of conception, it is given

TABLE II. PREMATURES LISTED IN ASCENDING ORDER OF VALUE OF PREMATURE SURVIVAL INDEX. THREE FACTORS OF INDEX INCLUDED

| CASE NO. | INDEX | GESTATION (WEEKS) | WEIGHT (OUNCES) | CROWN-HEEL LENGTH (INCHES) | TIME SURVIVED |
|----------|-------|----------------------|--------------------|----------------------------------|------------------|
| 11 | 19.2 | 27 | 35.5 | 14.8 | 39 hours |
| 3 | 19.4 | 28½ | 35.5 | 14.4 | Living |
| 15 | 19.8 | 28½ | 36.0 | 15.25 | Living |
| 6 | 20.4 | 28 | 36.0 | 15.0 | Living |
| 23 | 20.5 | 27 | 40.0 | 16.25 | 4 hours |
| 10 | 20.7 | 28 | 41.0 | 15.0 | 11 hours |
| 20 | 20.7 | 32½ | 38.0 | 14.25 | Living |
| 22 | 20.8 | 28 | 41.0 | 15.25 | 4½ hours |
| 14 | 21.0 | 28 | 42.0 | 15.5 | Living |
| 21 | 21.4 | 32 | 39.0 | 16.25 | Living |
| 8 | 21.7 | 29½ | 43.0 | 16.0 | Living |
| 9 | 23.1 | 29¾ | 49.0 | 15.5 | Living |
| 4 | 23.3 | 29½ | 51.0 | 16.0 | Living |
| 13 | 23.3 | 30½ | 48.0 | 17.0 | Living |
| 16 | 24.6 | 32¾ | 52.5 | 16.5 | Living |
| 2 | 25.6 | 33½ | 57.0 | 15.6 | Living |
| 5 | 25.7 | 29½ | 60.5 | 16.5 | Living |

every opportunity to live that expert pediatric care can afford. As seen in Table II, some of the smallest infants can be reared, and it seems impossible to predict from weight exactly which ones will survive.

Our aim is to continue with this problem until we obtain a large series from which positive conclusions can be drawn. We should be able eventually to say that every premature infant above a certain level should be reared. Furthermore, it should be possible to determine probable survival rates for each group below this level. Such predictions should be possible in the absence of congenital anomalies, obstetric accidents, individual maternal variations, maternal diseases, etc. Similar curves have been produced for some of the commonly used individual factors, but we are convinced that a five-point index will produce a much more accurate picture, a more composite spot graph, than produced from any single factor.

What has been said up to this point is almost strictly in the realm of pediatrics. The obstetrician is interested in this problem primarily from the point of having a concise, reasonably accurate graph from which he may determine the chance of survival of a prematurely born child. Most of these premature labors will be unavoidable in that labor cannot be stopped even with heavy sedation in their earliest phases. However, occasionally he will have charge of a maternal disease which is detrimental to mother and/or child, and he is anxious to know the probability of survival of the child if labor is induced.

We are of the considered opinion that the obstetrician's interest in premature labor must be much deeper than these academic statistical probabilities. That the mortality rate for prematurely born children has fallen markedly in the past decade is too well known to require elaboration. It is perhaps not as well known, or as freely admitted, that practically all this credit, in general, must go to the pediatrician, not the obstetrician. The modern, well-equipped, well-staffed premature nursery has apparently almost reached its irreducible premature mortality rate. Beyond a shadow of a doubt, such a nursery could make an even better showing if it were provided with better material. We

do not now have reference to material equipment, but to the quality of the premature infant delivered to that nursery. Obviously, not every prematurely born child is alive and in good condition when presented to this *milieu* for which its respiratory and gastrointestinal tracts in particular are not equipped. Certainly, the accoucheur cannot be blamed for a congenital anomaly incompatible with life nor for a breech position which is far less compatible with life for the premature infant than any vertex position. On the other hand, one does not have to dig deeper than the records of the current series to find suggestions for improving the quality of the newborn premature infant.

It has often been said that the most important phases of obstetric attention are pre- and postnatal care and that anybody can deliver the child. We cannot deny that the actual delivery is too often dramatized far beyond its true importance. Most parturients will deliver themselves spontaneously and safely within limits with major interference not often imperative when dealing with term or near term pregnancies. This is far from true when the case is one of premature labor. To be sure, proper prenatal care is the *sine qua non* of prophylactic treatment of premature labor. But there are few phases of obstetric care which require greater skill in plotting and greater determination in carrying out the course than does the management of premature labor and of premature delivery if the obstetrician is going to play a part in reducing the premature mortality rate.

The conduct of premature labor and delivery call for few and for rather simple principles. These are primarily concerned with the avoidance of drugs which will interfere with the initiation and continuation of respirations in the newly born premature infant and with protection of the excessively malleable fetal head. Few object to the use of even heavy sedation in the event of threatened premature labor or possibly even in apparent very early premature labor. Analgesics are all respiratory depressants and must be avoided after the onset of true labor in the period of prematurity lest resuscitation be required at delivery or stimulation necessary thereafter. Exactly the same must be said for inhalation anesthetics. The latter are unnecessary since local and regional anesthetics are admirable substitutes. We have found no mothers unwilling to tolerate premature labor without analgesia and without inhalation anesthesia if the problems are properly presented. Each has been willing to accept whatever pain may be required to afford her anticipated premature infant the best possible chance of survival. We should interject here that the pediatrician finds greatest satisfaction, when dealing with premature infants, in receiving those whose respirations have not been hampered.

One of the best means of protecting the premature infant's excessively malleable head is to preserve the integrity of the fetal membranes as long as possible, even through the second stage of labor. This is frequently impossible for premature labor is often initiated by spontaneous premature rupture of the membranes, this event having occurred in nine of the 23 cases in this series. Finally, if one is dealing with a more or less rigid lower birth canal or perineum, the use of low forceps properly applied and/or episiotomy is considered good obstetrics designed to protect the fetal head from molding beyond its safe limits. In this connection, it might be pointed out again that in case 19 of the

current series a fetus of a 30½ weeks' gestation was delivered spontaneously with episiotomy, after an eight-hour labor, the premature infant succumbing, after sixteen hours, to extensive intracranial damage.

The premature infant needs all the blood that it can bring with it into its new environment. Microcytic hypochromic anemia is common in the premature infant because of the low storage of iron and its decreased ability to metabolize iron. For this reason, it is ideal to delay clamping and cutting of the umbilical cord until the cessation of pulsations in its vessels.

Finally, the pediatrician has been impressed with the advantage of the use of chemotherapy in the newly born premature infant for he frequently, if not routinely, employs penicillin prophylactically even in the absence of any evidence of antenatal or intrapartum maternal infection. Recent bacteriological studies of the oronasal cavities of newborn infants⁹ suggest the routine use of chemotherapy in all premature labors, certainly in all with ruptured membranes.

With these facts in mind, it appears that there is no obstetric-pediatric problem which requires closer cooperation between representatives of these two branches of medicine than does that of premature labor. Certainly, this is true if the obstetrician is going to play his rightful role in reducing the premature mortality rate to an irreducible level.

Conclusions

1. The absence of a universally acceptable standard for what constitutes a premature infant is deprecated.

2. Basic definitions for prematurity and for abortion are reiterated.

3. Various individual criteria for the diagnosis of prematurity are reviewed and reasons given for their inaccuracies when employed separately.

4. A five-point premature survival index is offered as a means of overcoming inaccuracies in individual criteria.

5. Application of this composite index to twenty-three premature newborns is presented.

6. Suggestions for the obstetrician's contribution in reducing the premature infant mortality rate are given. These include: avoidance of analgesia after the onset of true labor in the period of prematurity, the use of local or regional anesthesia for premature delivery, preservation of the integrity of the fetal membranes through the second stage of labor, maintenance of maternal-fetal circulation as long as possible, and the prophylactic use of chemotherapy in premature labor.

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LATE DYSTOCIA TREATED BY THE NORTON EXTRAPERITONEAL CESAREAN SECTION

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DYSTOCIA recognized late in labor or after failure of attempted vaginal delivery poses the problem of a safe termination. Transperitoneal cesarean section at this stage is hazardous because it is accompanied by a high maternal mortality from peritonitis.¹ Traumatic vaginal delivery with or without fetal destructive operations,² even in multiparas, has proved disastrous to the fetus, and caused a high maternal mortality.³

Dieckmann⁴ prefers cesarean hysterectomy, despite its high maternal mortality (1 to 14 per cent), in all such "neglected" cases instead of extraperitoneal cesarean section. He claims that frequent peritoneal tears incurred during the latter operation defeat the purpose of the extraperitoneal route. On the other hand, Cosgrove and Waters⁵ maintain, and quote others that hold likewise, that small peritoneal tears sustained during the extraperitoneal operation repaired before incising the uterus do not contribute to increased maternal morbidity or mortality.

There are two generally accepted methods of extraperitoneal approach to the lower uterine segment. They are the Physick-frank-Sellheim supravescical approach elaborated by Waters^{6, 7} and Ricci,⁸ and the Latzko⁹ paravesical approach advocated by Burns.¹⁰ Norton¹¹ more recently described a paravesical extraperitoneal cesarean section which simplifies and facilitates the operative technique. Its most outstanding feature is its performance by *blunt* dissection of the fascial investments of the bladder, thus reducing to a minimum injuries to that organ. It also provides for *blunt* partial separation of the peritoneal folds from the uterus and bladder, and eliminates frequent peritoneal injuries.

We followed the technique outlined by Norton¹¹ in the treatment of dystocia late in labor, and briefly stated it is as follows:

1. The bladder is distended with about 200 c.c. of tinted fluid. Under fractional spinal anesthesia a left paramedian incision is made through the skin and superficial fascia. The upper point of the incision is two centimeters above the visibly distended bladder, and the lower point at the pubic tubercle. The left anterior rectus sheath is incised and the left rectus muscle is detached from the midline.

2. The left paravesical space is exposed by upward and outward retraction of the left rectus muscle (Fig. 1). In this space a layer of "chicken yellow fat" is identified. Blunt dissection of the anterior fascial investments of the bladder (i.e., transversalis fascia and anterior vesical fascia) is begun at this point. The detached fascia is incised downward and to the right (Fig. 2); the starting point of this procedure is at the junction of the upper and middle third of the left border of the distended bladder, where usually the deep epigastric vessels enter the left rectus muscle (Fig. 1). This detail is important in order to prevent injury to the anterior fold of peritoneum above, if the dissection is begun higher, or to the vesical trigone and ureter, if the separation is commenced lower.

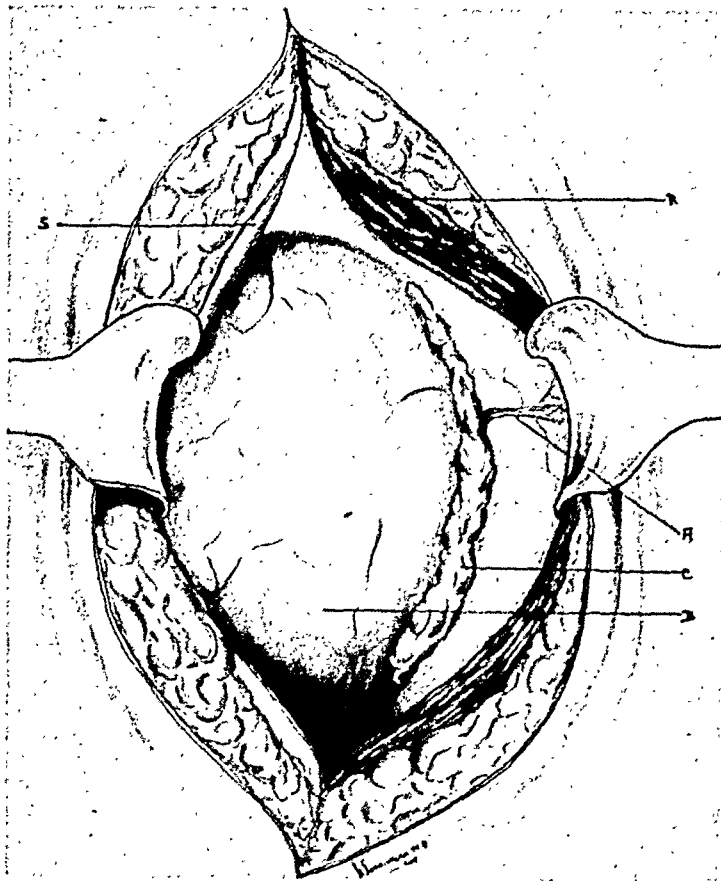


Fig. 1.—Exposure of the left paravesical space. *A*, deep epigastric vessels; *B*, distended bladder; *C*, chicken yellow fat; *S*, left rectus fascia; *R*, left rectus muscle.

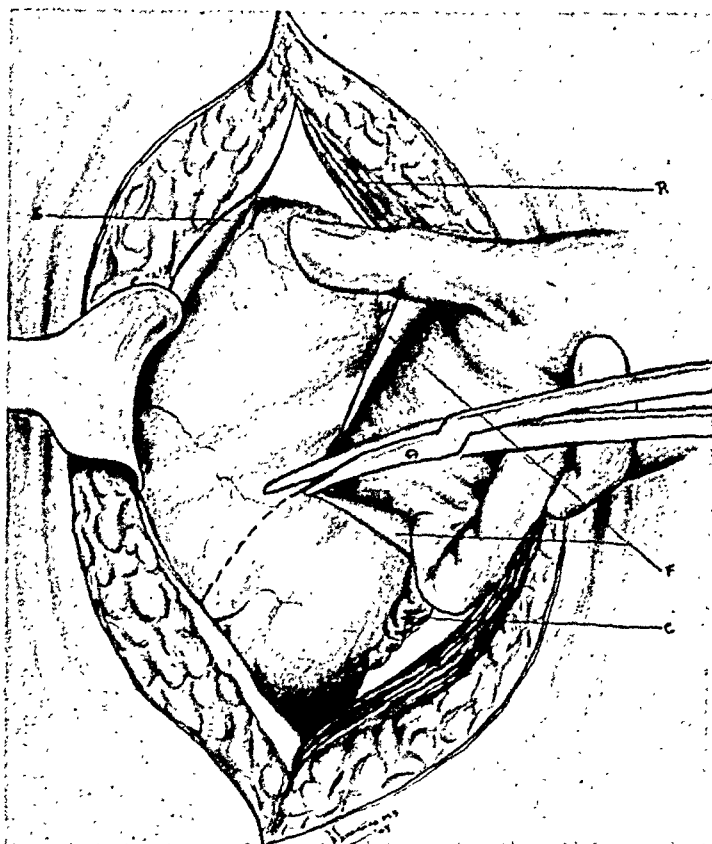


Fig. 2.—Detachment and incision of the transversalis and anterior vesical fasciae. *C*, chicken yellow fat; *S*, left rectus fascia; *R*, left rectus muscle; *F*, transversalis and anterior vesical fasciae, bluntly detached and incised downwards and to the right.

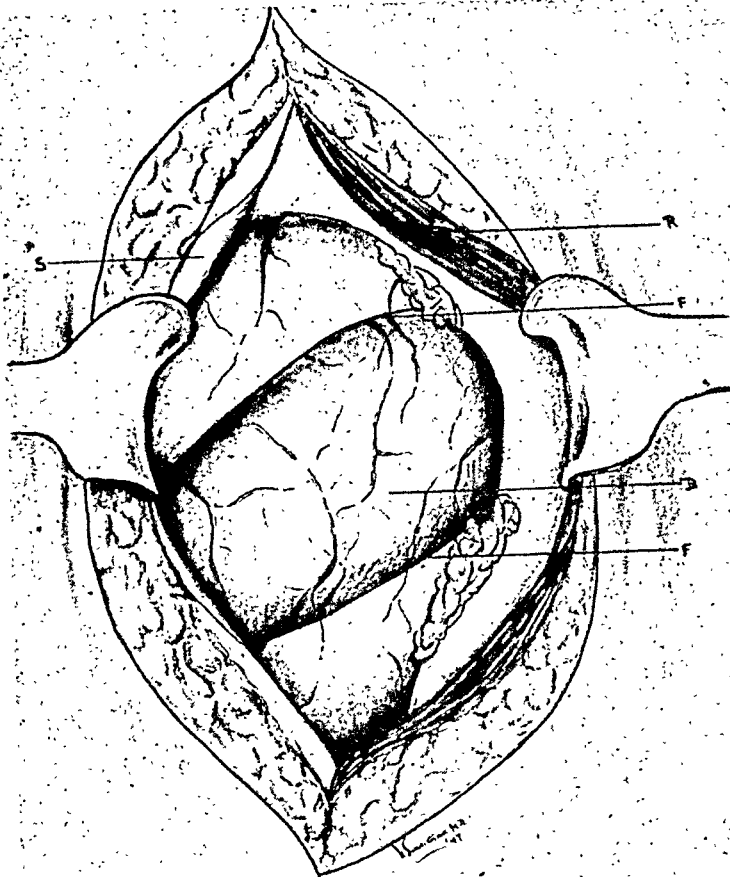


Fig. 3.—Herniation of the bladder through the cut fasciae. *B*, distended bladder; *F*, cut edges of transversalis and anterior vesical fasciae; *S*, left rectus fascia; *R*, left rectus muscle.

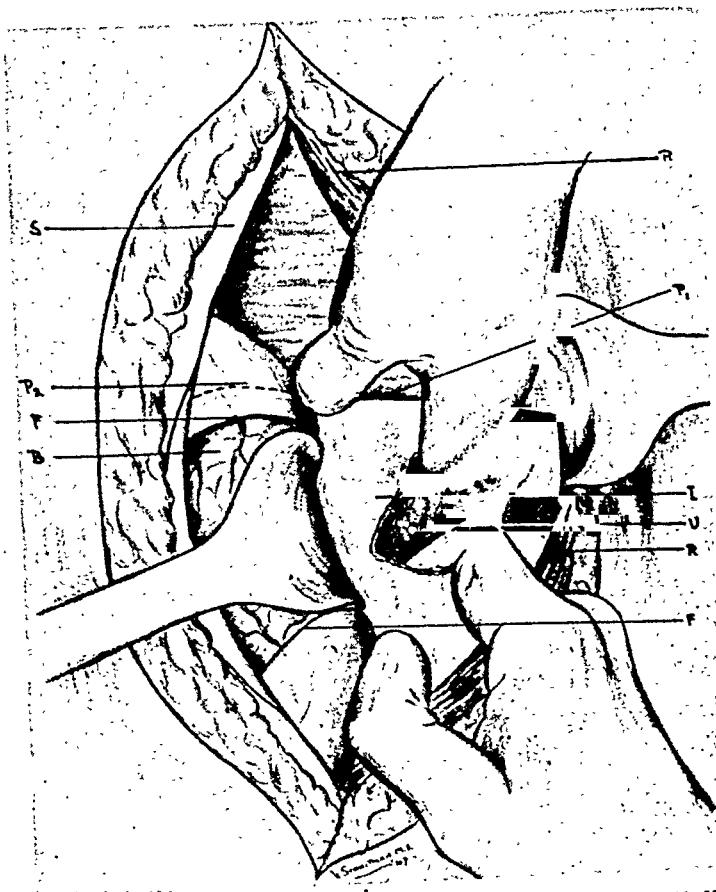


Fig. 4.—Exposure of the retrovesical triangular area. *B*, partially emptied bladder; *S*, left rectus fascia; *R*, left rectus muscle; *F*, incised transversalis and anterior vesical fasciae; *P1*, posterior peritoneal fold; *P2*, location of anterior peritoneal fold; *R*, *B*, *P1*, outline triangular area in which *I*, the retrovesical, and periuterine fasciae are incised exposing *U*, the lower uterine segment.

3. With the bladder freed of its fasciae anteriorly permitting its herniation (Fig. 3) in its midportion and partially emptied of fluid, it is detached posteriorly by blunt dissection in the left paravesical space from the lower uterine segment sufficiently to expose a triangular area (Fig. 4). This triangular area is formed by the left rectus muscle laterally, the left margin of the partially distended bladder medially, and the posterior peritoneal fold above.

4. A small transverse incision is made in the floor of this triangle (Fig. 4) about two centimeters below the visible posterior peritoneal fold through the retrovesical and periuterine fascial layers. This incision is enlarged by the insertion of retractors and further expanded by blunt dissection to permit detachment of the peritoneum and bladder from the lower uterine segment (Fig. 5). During this procedure the bladder is gradually emptied of its fluid and pulled to the right and downward, being protected from injury by the posterior fascial sheaths. The posterior peritoneal fold is pulled upward and likewise protected from tearing by the same fascial sheaths (Fig. 5).

5. The exposed lower uterine segment is then incised either transversely in a semilunar fashion or longitudinally (Fig. 6).

6. After delivery of the fetus and placenta, oxytocics are administered. The uterus is closed with two layers of chromic sutures (Fig. 7), and all bleeding points are carefully controlled.

7. The peritoneum is inspected for perforation by permitting the patient to cough or strain. The integrity of the bladder is tested by refilling it with tinted fluid, and it is allowed to return to its original site. Finally, a cigarette drain is inserted between the bladder and the uterine incision (Fig. 7).

8. The muscle, anterior rectus sheath, superficial fascia, and skin are closed in layers with the drain emerging from the lower angle of the wound (Fig. 7).

We have performed this operation and followed the above technique in thirty-five cases (Table I). All the operations were done in instances where prolonged labor, many hours of ruptured membrane, frequent vaginal examinations, and intrapartum morbidity made the patients potentially and/or actually infected. However, we have also included in this series three patients who required abdominal delivery, but were not infected. The latter were done electively by the extraperitoneal technique to familiarize ourselves with the steps outlined above.

Table I reveals that extraperitoneal cesarean section was indicated in fifteen cases because of fetopelvic disproportion recognized late in labor. All of these patients were considered to have had ample and/or borderline pelvic measurements as evaluated by pelvic mensuration with calipers, clinical appraisal of the pelvis, and Hillis test. Antepartum x-ray pelvimetry of one patient disclosed an ample pelvis with no disproportion, and of two others with borderline measurements. Intrapartum x-ray pelvimetry exhibited one patient with an ample pelvis, one with a borderline pelvis, and three with absolute fetopelvic disproportion. In the remaining seven cases no x-ray pelvic studies were undertaken either antepartum or intrapartum. In all of these instances adequate tests of labor with unsatisfactory progress convinced us that pelvic delivery would produce poor results, and abdominal operation was decided upon.

In seven cases the operation was done for apparent cervical dystocia. In all, the pelvis was considered ample by clinical appraisal; two had antepartum and one intrapartum x-ray pelvimetry to confirm pelvic adequacy. Strong labor with lack of progress in softening and dilating the cervix, despite engagement of the presenting part convinced us that the cervix was unyielding. These patients were in labor from eighteen to forty-seven hours with ruptured mem-

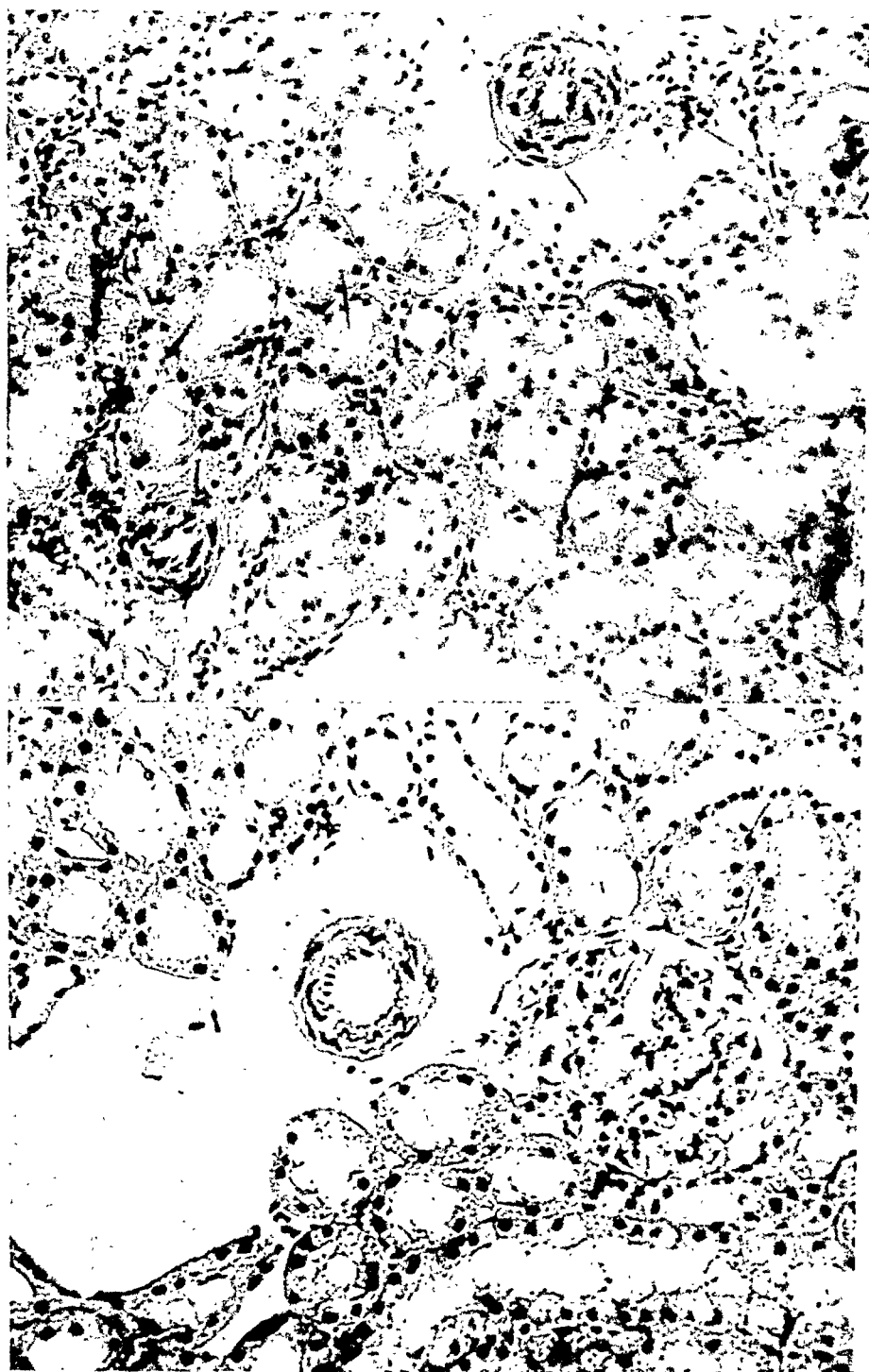


Fig. 1.—Kidney tissue obtained by biopsy three days postpartum from rat No. 4. Note the thickening of the walls of the two arterioles and the reduction of their lumens. The outer circumference of the larger arteriole measured four microns.

Fig. 2.—Kidney tissue obtained by biopsy three days postpartum of a control litter mate of rat No. 4 which had no previous treatment of placental suspension. Note the normal thickness of the wall of the arteriole. The outer circumference of this arteriole also measured four microns.

TABLE I. SUMMARY OF CASES TERMINATED BY NORTON EXTRAPERITONEAL CESAREAN SECTION

| INDICATIONS | CASE NO. | PARTY | | HOURS OF LABOR | HOURS OF RUPTURED MEMBRANES | INTRA-PARTUM TEMPERATURE | NO. OF EXAMINATION | | PREOPERATIVE VAGINAL MANIPULATION | BLADDER INJURY | PERITONEAL INJURY | HOSPITAL DAYS | RESULT | | WEIGHT OF FETUS IN GRAMS |
|---------------------------------|----------|-------|-------|----------------|-----------------------------|--------------------------|--------------------|---|-----------------------------------|----------------|-------------------|---------------|-----------|-----------|--------------------------|
| | | PARA. | GRAV. | | | | R | V | | | | | MATERNAL. | FETAL | |
| Elective | 1 | 0 | iii | 0 | 0 | Normal | 1 | 0 | None | None | None | 10 | Cured | Living | 2013 |
| | 2 | 0 | i | 5 | 0 | Normal | 1 | 0 | None | None | None | 12 | Cured | Living | 3544 |
| | 3 | 0 | i | 5 | 5 | Normal | 1 | 0 | None | None | None | 9 | Cured | Living | 2807 |
| Potopelvic disproportion | 4 | 0 | i | 27 | 79 | Normal | 3 | 0 | None | Yes | None | 12 | Cured | Living | 3204 |
| | 5 | 0 | i | 19 | 19 | Normal | 5 | 1 | None | None | None | 9 | Cured | Living | 2977 |
| | 6 | 0 | i | 54 | 54 | Normal | 6 | 1 | None | None | None | 9 | Cured | Living | 2977 |
| | 7 | 0 | i | 5 | 22 | Normal | 1 | 0 | None | None | None | 8 | Cured | Living | 3402 |
| | 8 | 0 | i | 35 | 35 | Normal | 7 | 0 | None | None | None | 10 | Cured | Living | 2693 |
| | 9 | 0 | i | 38 | 38 | Normal | 2 | 0 | None | None | None | 7 | Cured | Living | 4196 |
| | 10 | 0 | i | 41 | 10 | Normal | 9 | 0 | None | None | None | 8 | Cured | Living | 2608 |
| | 11 | 0 | i | 29 | 26 | Normal | 9 | 0 | None | None | None | 12 | Cured | Living | 4366 |
| | 12 | 0 | i | 28 | 1 | Normal | 7 | 0 | None | None | Yes | 9 | Cured | Living | 2920 |
| | 13 | 0 | i | 20 | 14 | Normal | 4 | 0 | None | None | None | 10 | Cured | Living | 3175 |
| | 14 | 0 | i | 33 | 20 | Normal | 9 | 0 | None | None | None | 10 | Cured | Living | 3345 |
| | 15 | 0 | i | 21 | 17 | Normal | 6 | 2 | None | None | None | 9 | Cured | Stillborn | 2807 |
| | 16 | 0 | i | 36 | 33 | Normal | 8 | 1 | None | None | None | 12 | Cured | Living | 3147 |
| | 17 | i | ii | 19 | 8 | Normal | 3 | 0 | None | None | None | 13 | Cured | Living | 4253 |
| | 18 | 0 | i | 6 | 48 | Normal | 3 | 0 | None | None | None | 7 | Cured | Living | 3090 |
| Cervical dystocia | 19 | 0 | i | 41 | 41 | 102.2° F. | 10 | 1 | None | None | None | 10 | Cured | Stillborn | 2977 |
| | 20 | 0 | i | 28 | 9 | Normal | 6 | 2 | Amniotomy | None | Yes | 10 | Cured | Living | 4309 |
| Uterine inertia | 21 | 0 | i | 30 | 54 | 101.0° F. | 7 | 1 | None | None | None | 8 hr. | Died | Living | 3459 |
| | 22 | 0 | i | 17 | 17 | Normal | 5 | 3 | Catheter Induction | None | None | 8 | Cured | Living | 3657 |
| | 23 | 0 | i | 47 | 47 | 103.2° F. | 9 | 1 | None | None | None | 10 | Cured | Living | 3175 |
| | 24 | i | iii | 35 | 35 | Normal | 4 | 1 | None | None | None | 12 | Cured | Living | 2608 |
| | 25 | iii | v | 36 | 35 | Normal | 10 | 2 | None | None | None | 16 | Cured | Living | 3317 |
| Malpresentation and malposition | 26 | 0 | i | 28 | 36 | Normal | 2 | 2 | None | None | None | 10 | Cured | Living | 3544 |
| | 27 | 0 | i | 42 | 42 | Normal | 10 | 1 | None | None | None | 8 | Cured | Living | 2637 |
| | 28 | 0 | i | 56 | 26 | 102.4° F. | 8 | 1 | None | None | None | 11 | Cured | Living | 3175 |
| | 29 | 0 | i | 160 | 160 | Normal | 3 | 3 | None | None | None | 13 | Cured | Living | 3004 |
| | 30 | 0 | i | 60 | 60 | 101.8° F. | 9 | 1 | None | None | None | 8 | Cured | Living | 2240 |
| Failed forceps | 31 | 0 | ii | 0 | 18 | Normal | 1 | 0 | None | None | Yes | 12 | Cured | Living | 3033 |
| | 32 | i | iii | 9 | 33 | Normal | 7 | 0 | None | None | None | 9 | Cured | Living | 3232 |
| | 33 | 0 | i | 61 | 61 | Normal | 6 | 2 | None | None | None | 14 | Cured | Living | 2495 |
| | 34 | 0 | i | 48 | 48 | 101.6° F. | 1 | 1 | None | None | None | 9 | Cured | Living | 3231 |
| | 35 | 0 | i | 16 | 2 | Normal | 5 | 1 | Failed forceps | Yes | None | 12 | Cured | Stillborn | 3090 |

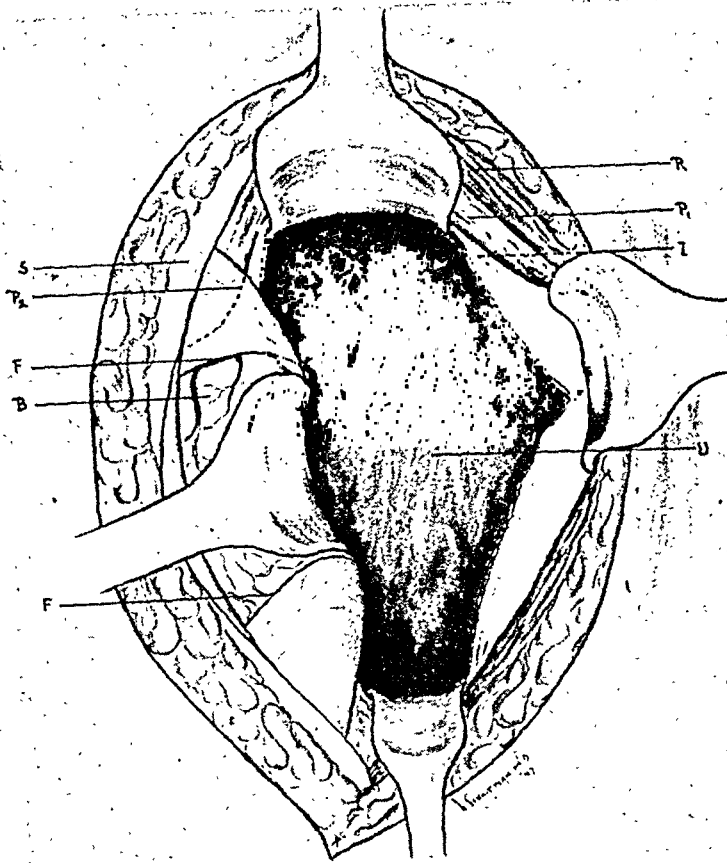


Fig. 5.—Enlargement of the retrovesical and infraperitoneal area of the lower uterine segment. *B*, retracted and almost emptied bladder; *S*, left rectus fascia; *R*, left rectus muscle; *F*, transversalis and anterior vesical fasciae; *P*₁, posterior peritoneal fold retracted upwards; *P*₂, anterior peritoneal fold attached to the fundus of the bladder and retracted to the right; *I*, retracted retrovesical and periuterine fasciae; *U*, lower uterine segment.

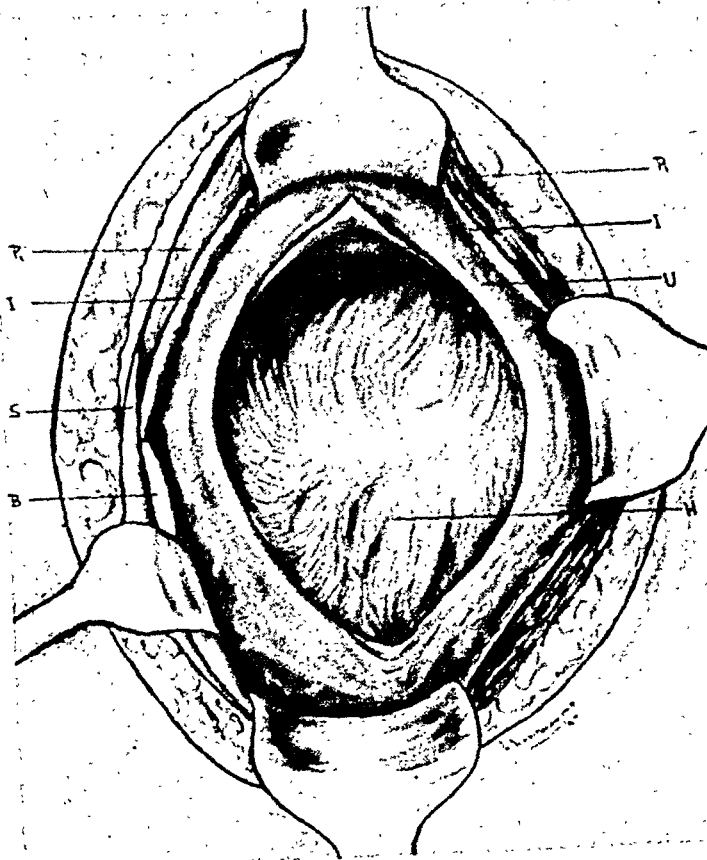


Fig. 6.—Uterine incision and delivery of the fetal head. *B*, completely emptied and retracted bladder; *S*, left rectus fascia; *R*, left rectus muscle; *I*, retrovesical and periuterine fasciae; *P*₁, retracted posterior peritoneal fold; *U*, longitudinally incised uterus; *H*, fetal head.

many hours of watchful expectancy correction did not occur. There were two brow presentations, one of which was in labor sixty-one hours with ruptured membranes for a similar length of time. The other brow presentation was forty-eight hours in labor with ruptured membranes occurring at the onset of labor. Both of these patients had reached 4 cm. dilatation, the presenting part was not completely engaged; one patient had an intrapartum temperature of 101.6° F. (Case 34, Table I). There was one case of transverse presentation (RScA, Case 31, Table I) in which the membranes were ruptured for eighteen hours and no labor had ensued. One patient had compound presentation (head and hand) discovered at operation. This was a multipara with unengaged vertex after thirty-three hours of ruptured membranes, nine hours of strong labor, and no progress in cervical dilatation above 3 cm. This patient previously had a breech delivery with difficulty of the aftercoming head. Although x-ray pelvimetry revealed pelvic adequacy, operation was decided upon when no descent of the presenting part occurred, despite nine hours of strong labor.

Failure of forceps with intrapartum fetal death (Case 35, Table I) which occurred during attempted vaginal delivery led us to terminate labor by extraperitoneal cesarean section rather than by a fetal destructive operation. This was a primipara who, after sixteen hours of labor and two hours of ruptured membranes, became fully dilated with the presenting part below the spines. After restoring this patient and putting her in good condition for surgery, she was delivered by the extraperitoneal route with a satisfactory maternal result.

The bladder was injured twice, or in 5.7 per cent of the cases. The rent was repaired immediately. The bladder was kept continuously empty and dry by suction with a retention catheter and a Stedman¹² pump for seven days postoperatively. Healing was complete after that time, and voiding was spontaneous. No urinary fistulae resulted.

The peritoneum was accidentally opened three times, or in 8.5 per cent of the series. This was closed with a simple ligature tie without suturing the peritoneal tear before the uterine cavity was opened. These injuries occurred only early in our experience with this operation.

The uterine cavity was entered in nineteen instances by a longitudinal incision and by a semilunar transverse incision in sixteen instances. The choice of the incision remains with the operator, depending upon conditions prevailing at the time of operation. There is less bleeding when the transverse semilunar incision is used, and there is less chance of injury to the peritoneal fold as a result of traction upward to permit an adequate longitudinal incision. In some instances the longitudinal incision is absolutely necessary. This is especially true when a constriction ring exists as in Case 29, Table I. Incising parallel to a constriction ring as in transverse semilunar incision makes for great difficulty in delivering the fetus.

There were three stillbirths in this series. One was a known fetal death prior to operation after failure of forceps. In one, the fetal heart sounds were slow (80 per minute) before operation after prolonged labor in a case of absolute fetopelvic disproportion discovered late in labor. The third stillbirth occurred in a patient with pre-eclampsia where the membranes were ruptured for forty-one hours with long labor, intrapartum elevated temperature, and thick meconium showing prior to operation. Upon delivery, the heart sounds were present but slow, and respirations could not be initiated. Those that survived weighed between 2,013 Gm. and 4,366 Gm. The average was 3,020 Gm.

Postoperative morbidity occurred in six patients, a rate of 17.1 per cent. Four patients were morbid for two days, one for four days, and one for five days; the remainder, or twenty-nine patients, were afebrile during their postpartum stay in the hospital.

branes for that many or even more hours (maximum fifty-four hours). Three patients (Cases 19, 21, and 23, Table I) had elevated intrapartum temperatures. The other four patients were considered infected because of numerous rectal and vaginal examinations or vaginal manipulations. In Case 20 membranes were ruptured artificially, and in Case 22 labor was induced for pre-eclampsia by insertion of catheters. Although sedation was used in most cases to prevent maternal exhaustion, the return of forceful labor pains made no appreciable progress in cervical dilatation. In all these cases the cervix remained thick and rigid, and in no case did it dilate beyond 5 cm. In one patient (Case 25) the maximum cervical dilatation obtained was 3 cm., despite thirty-six hours of strong labor and ruptured membranes for thirty-five hours. This patient was a multipara who had a previous uterine suspension and trachelorrhaphy.

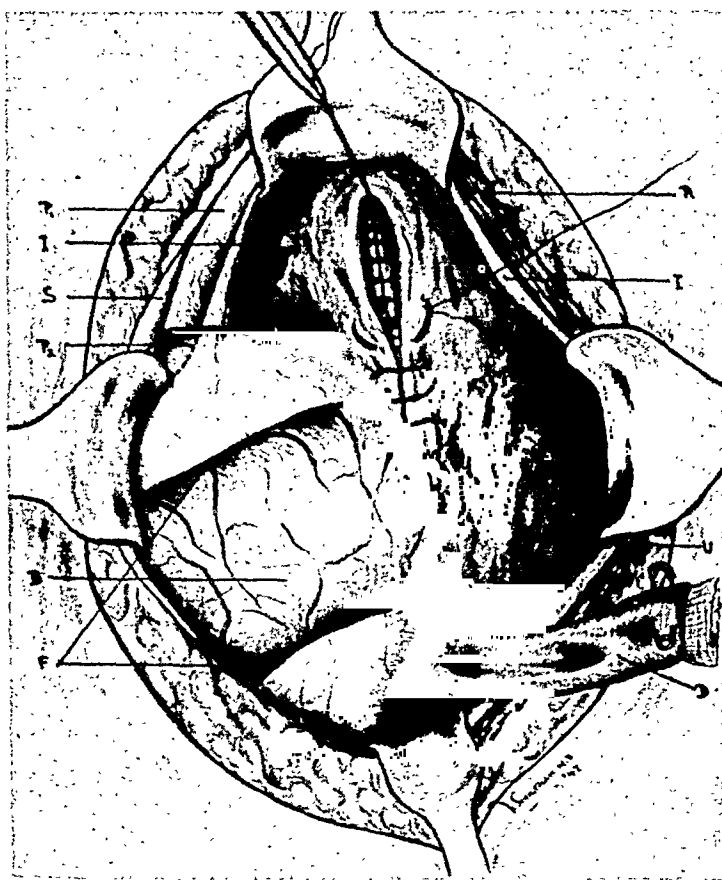


Fig. 7.—Uterine closure, testing integrity of bladder, peritoneum and insertion of drain. *U*, uterus being closed in two layers; *B*, refilled bladder; *F*, Transversalis and anterior vesical fasciae; *S*, left rectus fascia; *R*, left rectus muscle; *P*₁, posterior peritoneal fold; *P*₂, anterior peritoneal fold; *I*, retrovesical and periuterine fasciae; *D*, cigarette drain.

There were five instances of uterine inertia. Four of these patients were considered to have no fetopelvic disproportion by clinical means and pelvic mensuration done ante partum. In the fifth patient fetopelvic adequacy was assured by x-ray pelvimetry. Labor lasted from twenty-eight hours to one hundred sixty hours, and the membranes were ruptured twenty-six hours to one hundred sixty hours. In all these cases dilatation of the cervix reached from 2 to 7 cm. In three cases the presenting part was not completely engaged, and in two instances the presenting part was at the ischial spines at the time of operation. Two of the patients (Table I, Cases 28, 30) had elevated intrapartum temperatures, and the other three were regarded as potentially infected.

In four cases operation was done for malposition. These were expected to correct themselves spontaneously with continued labor and time. After

ADENOCARCINOMA ARISING IN AN ENDOMETRIAL CYST OF THE OVARY

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ADENOCARCINOMA arising in an endometrial cyst of the ovary is an unusually rare gynecologic finding. Sampson¹⁵ originally reported this condition more than twenty-two years ago, but to our knowledge only one other similar case has appeared in the literature.

Since the incidence of endometriosis is high (26 to 43 per cent),^{5, 8, 13} it would seem that carcinomatous change should be found more frequently. Such neoplasia has been reported in endometrial cysts of the Fallopian tube, the serosal surface of the uterus,^{4, 12} and from endometriomas in the rectovaginal septum.^{19, 20} Indeed one of us (D.M.G.)³ has seen carcinoma arising in an adenomyoma of the uterus.

Sampson's¹⁵ unique case of carcinoma arising from a benign cyst of the ovary was not associated with malignancy in the uterus or Fallopian tubes. He postulated rigid criteria for the proof of the endometrial origin of such a tumor. These were: (1) the coexistence of benign and malignant tissue in the same ovary which have the same histologic relationship to each other as in carcinoma of the body of the uterus; (2) the carcinoma must actually be seen arising in this tissue, and not invading it from some other source; (3) additional supportive evidence includes the attendance of tissue resembling endometrial stroma about characteristic epithelial glands and the finding of old hemorrhage rather than fresh, since the latter can be the result of trauma accruing from surgical manipulation. These criteria are difficult to meet, since the carcinoma arising in benign ectopic endometrial tissue usually obscures and replaces it completely, thus hiding evidence of its origin. It is interesting to note that Novak and Goodall¹⁴ accepted only one of Sampson's four purported cases of carcinoma arising from pre-existing endometrioma of the ovary. They thought that in the other three cases the malignancy most probably arose from cystadenomata present in the ovary. Teilum¹⁷ recently described another case of adenocarcinoma arising in an endometrial cyst of the ovary.

In this connection, Graves² suggested that some papillary cystadenomata of the ovary are in reality malignant endometriomata growing from aberrant implants of uterine mucosa. However, he offered no supportive evidence for this assumption. Frank¹ and Meyer⁹ are not convinced of such malignant transformations. Novak¹¹ has pointed out the similarity between some serous papillary cystadenocarcinomas to adenocarcinoma of the endometrium. He felt that this might be evidence in favor of Sampson's theory, but that it probably befitted only a small proportion of ovarian malignancies. Taylor¹⁶ also agreed with the theory of origin of ovarian carcinoma from endometrial growths in the ovary which are similar to uterine mucosa. He was not certain, however, whether the endometrial growths represented transplanted uterine mucosal tissue or germinal epithelium, since both are closely akin and originate from celomic epithelium. Consequently he made no distinction between "endometrial carcinoma" and "germinal epithelium carcinoma" of the ovary. Norris

Four patients had postoperative complications; two had excessive wound drainage, one had marked abdominal distention, and one had massive pulmonary embolism which occurred eight hours postoperative and proved fatal.

Summary

1. Employment of transperitoneal cesarean section in the treatment of late dystocia results in a high maternal mortality due to peritonitis. Vaginal delivery with or without fetal destructive operations, to avoid the above results, proves disastrous to the fetus and produces severe maternal trauma and even death. Cesarean-hysterectomy is a formidable shocking procedure late in labor, and also contributes to a high maternal mortality.

2. A knowledge of the extraperitoneal approach for abdominal delivery should be in the armamentarium of every obstetric surgeon. Its application in late dystocia is a conservative and safe method of termination of labor. The Norton paravesical extraperitoneal approach, in our hands, has proved easy to master. Its outstanding advantage is that it is performed entirely by *blunt* dissection. Very early in our experience we injured the peritoneum three times and the bladder twice. There have been no injuries to either structure since.

3. The Norton technique was employed electively in three patients to better familiarize ourselves with the landmarks and steps of the operation. It was indicated in fifteen cases for fetopelvic disproportion, in seven patients for cervical dystocia, in five instances for uterine inertia, in four cases for malposition and malpresentation, and once in a case of failed forceps.

4. There were three stillbirths. One was a known intrauterine death resulting from failed forceps. The others showed fetal embarrassment prior to commencement of the operation. The average weight of the babies delivered was 3,020 Gm.

5. The postoperative course was usually smooth. The incidence of morbidity was low. One maternal death occurred eight hours after operation from massive pulmonary embolism.

We are thankful to Doctors Graves, Siegler, and Weitzman for permission to include the cases operated upon at the Harbor, Coney Island, Madison Park, and Brooklyn Womens Hospitals.

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Fig. 1.—Section of cyst wall showing cylindrical lining cells (hematoxylin-eosin, $\times 600$).

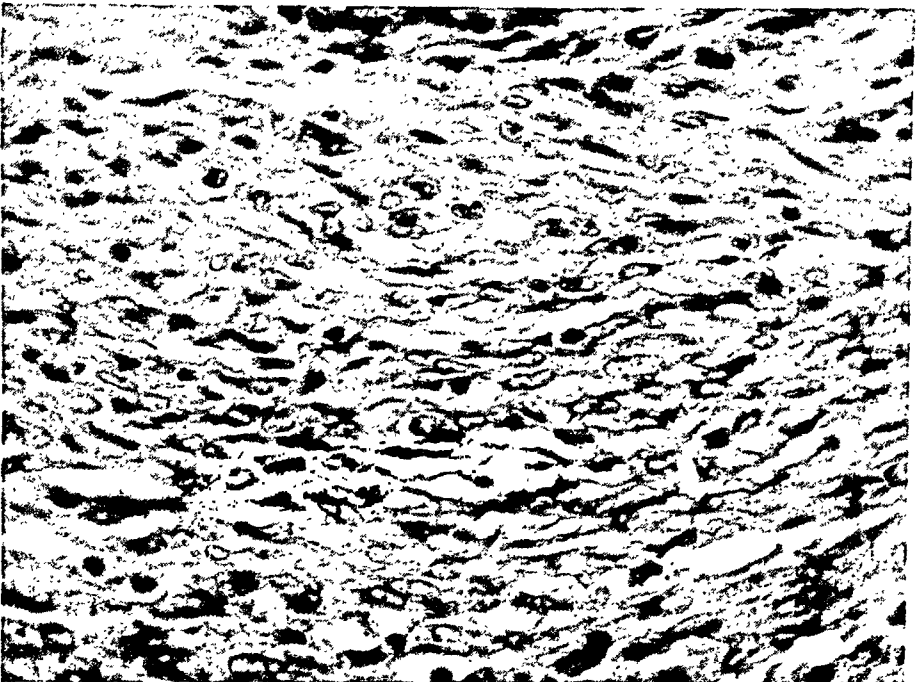


Fig. 2.—Section of cyst wall beneath epithelial layer shown in Fig. 1 showing endometrium-like stroma (Hematoxylin-eosin, $\times 600$).

and Vogt¹⁰ believe the prognosis more favorable in malignant degeneration of a benign cyst than in primary malignant tumors of the ovary.

Recently malignancies other than adenocarcinoma have been reported arising from benign endometrial cysts of the ovary.

McCullough, Froats and Falk⁷ described an epidermoid carcinoma arising from an endometrioma of the ovary. Kuzma⁶ reported two cases of ovarian adenoacanthoma developing in association with endometriosis of the ovary, but in only one of his cases is the evidence indisputable. Tuthill¹⁸ described a most unusual carcinosarcoma arising from an endometrioma of the ovary. The diagnosis was based on the presence of endometrial glands and stroma in the cyst wall showing early malignant changes and resembling carcinoma of the uterine mucosa.

Our interest in this subject was stimulated by the unusual case described below. The diagnosis of adenocarcinoma arising from a previous benign endometrial implant in the ovary was arrived at only after extended study. All of Sampson's postulates were met including the subsidiary findings of old hemorrhage in the cyst wall. Thus, this case represents the third example of adenocarcinomatous transformation in a benign endometrial cyst of the ovary to be reported.

Case Report

The patient was a 42-year-old white female first seen on Feb. 13, 1947, with an asymptomatic mass in the abdomen.

Catamenia began at 13 years of age, recurred every twenty-eight days, with a three- to five-day flow. The last menstrual period was on Feb. 2, 1947. The patient was a gravida ii, para ii, with two full-term pregnancies, normal in character.

The past history revealed an essential hypertension and the removal of an ovarian cyst seventeen years previously, in another hospital. The nature of the cyst could not be determined, since the record had been destroyed.

Physical examination revealed a well-developed, well-nourished female with a blood pressure of 190/105. The abdomen showed an old well-healed midline scar. Pelvic examination revealed a parous scarred introitus. The cervix was lacerated and hypertrophied. The uterus was anterior to a large cystic mass which was fixed, nontender, and extended three fingerbreadths above the umbilicus.

The patient was admitted to the Jewish Hospital of Brooklyn for surgery on Feb. 16, 1947. Laboratory work-up revealed no unusual findings in the urine or blood.

At operation, through a midline suprapubic incision, a large cyst the size of a sixteen weeks' gestation was found in the right lower abdomen arising from the right ovary. It was posterior to the uterus and chocolate in color. Several loops of small bowel were adherent to the cyst, and the latter was firmly adherent at its lower pole to the uterus. The adhesions were separated and a supracervical hysterectomy and right salpingo-oöphorectomy was performed. The left Fallopian tube and ovary were surgically absent. She made an uneventful recovery, and was discharged on her twelfth postoperative day.

The patient was seen two weeks later, and her pelvis presented no masses other than a free cervical stump.

Pathological Findings.—*Gross:* The surgical specimen consisted of a misshapen uterus which had been amputated above the cervix. It measured roughly 10 by 7.5 by 5 cm. There were two subserous leiomyomas which measured up to 1.2 cm. in greatest diameter. The uterine cavity was 6.8 cm.

in length, and it contained a soft polyp 2 cm. in length which was attached by a narrow pedicle; the tip was hemorrhagic. The endometrium was gray and clearly demarcated from the myometrium. The latter measured up to 2.1 cm. in thickness, and was moderately firm in consistency. Tiny lumina could be seen in the cut surfaces.

Accompanying this was an open cyst with an attached Fallopian tube. The cystic mass was said to be the right ovary, and it measured 21.3 by 11.5 cm. Its wall was gray or hemorrhagic in places, and measured up to 0.6 cm. in thickness. Lining the inner surface of the cyst was viscid dark brown material as well as soft, friable, yellow-red tissue. No normal ovarian tissue could be identified. The Fallopian tube did not appear unusual.

Microscopic: The section of the uterus showed the surface to be lined by slightly hyperplastic endometrium in the proliferative phase. Scattered throughout the myometrium were small islands of endometrial inclusions which were lined by well-preserved cylindrical cells. Most of these foci of adenomyosis were accompanied by a good amount of endometrial stroma, although in some places glandular inclusions without stroma were seen.

Section of the polyp showed it to be composed of endometrial glands supported by a delicate fibrous stroma.

Section of the Fallopian tube showed the usual corrugated lining and muscular wall. No endometrial inclusions were found.

Section of the cyst showed a thick fibrous wall which was moderately vascularized. Scattered diffusely throughout were small and large mononuclear cells as well as occasional plasma cells. A few polymorphonuclear leucocytes were also seen. The inner lining was disorganized in most places but frequently one could make out a thin layer of cylindrical cells which resembled those lining the endometrium. These were thrown into delicate corrugations and occasionally dipped down into the stroma in glandlike formation. The stroma here appeared denser and composed of thin spindle-shaped cells, similar to those appearing in the endometrium. Within the wall were also seen large macrophages containing blood pigments as well as small extravasations of blood.

Sections taken from the friable portion of the cyst showed a necrotic stroma in which were masses of atypical cylindrical cells. These cells were heaped up and hyperchromatic and the nuclei varied markedly in size and shape. Mitotic figures were present. Tumor cells extended into the lumen but did not break into the deeper layers of the cyst wall. The tumor cells often arranged themselves about lumina or along delicate stalks in glandlike or papillary formation.

Summary

1. The rarity of adenocarcinoma arising in an endometrial cyst of the ovary is noted.

2. The literature and requirements for the proof of an endometrial lesion of the ovary undergoing malignant change are reviewed.

3. A case presenting all the criteria for adenocarcinoma arising in an endometrial cyst of the ovary has been described.

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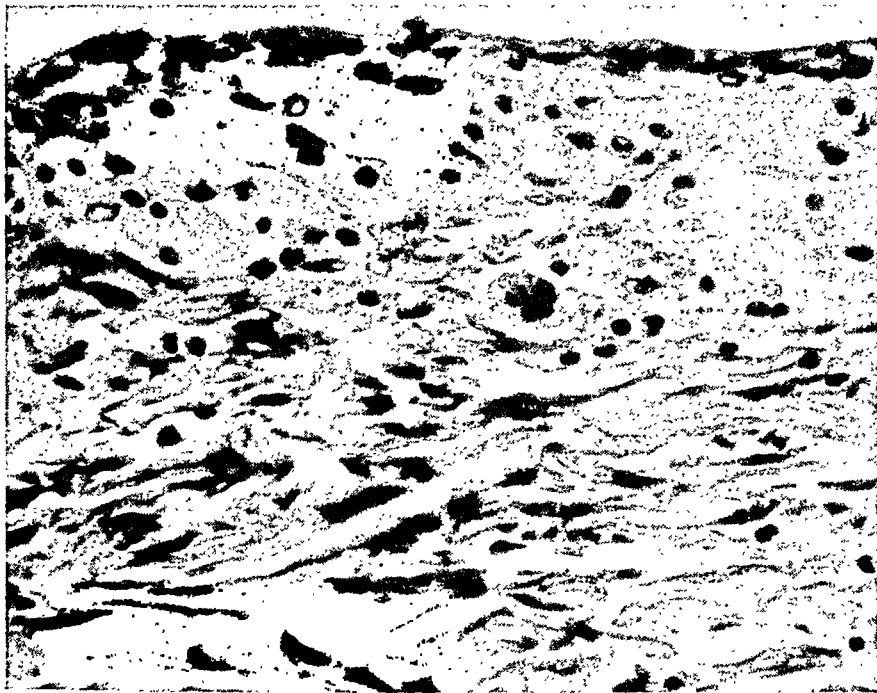


Fig. 3.—Section of cyst wall showing phagocytic cells containing blood pigment granules. Surface is denuded of epithelium (Hematoxylin-eosin, $\times 600$).

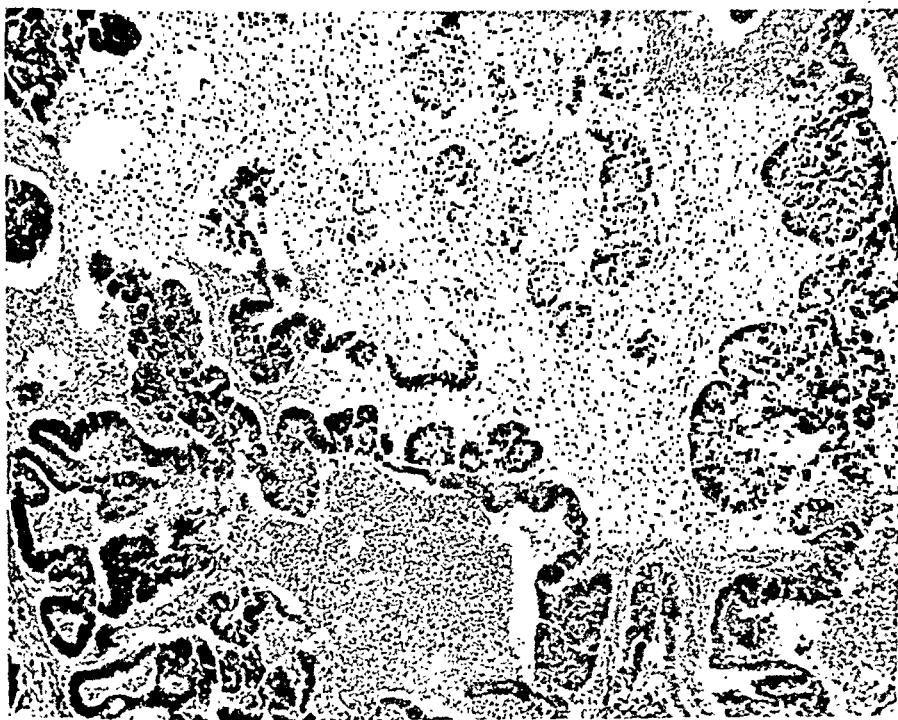


Fig. 4.—Section of adenocarcinomatous area in cyst lining (Hematoxylin-eosin, $\times 75$).

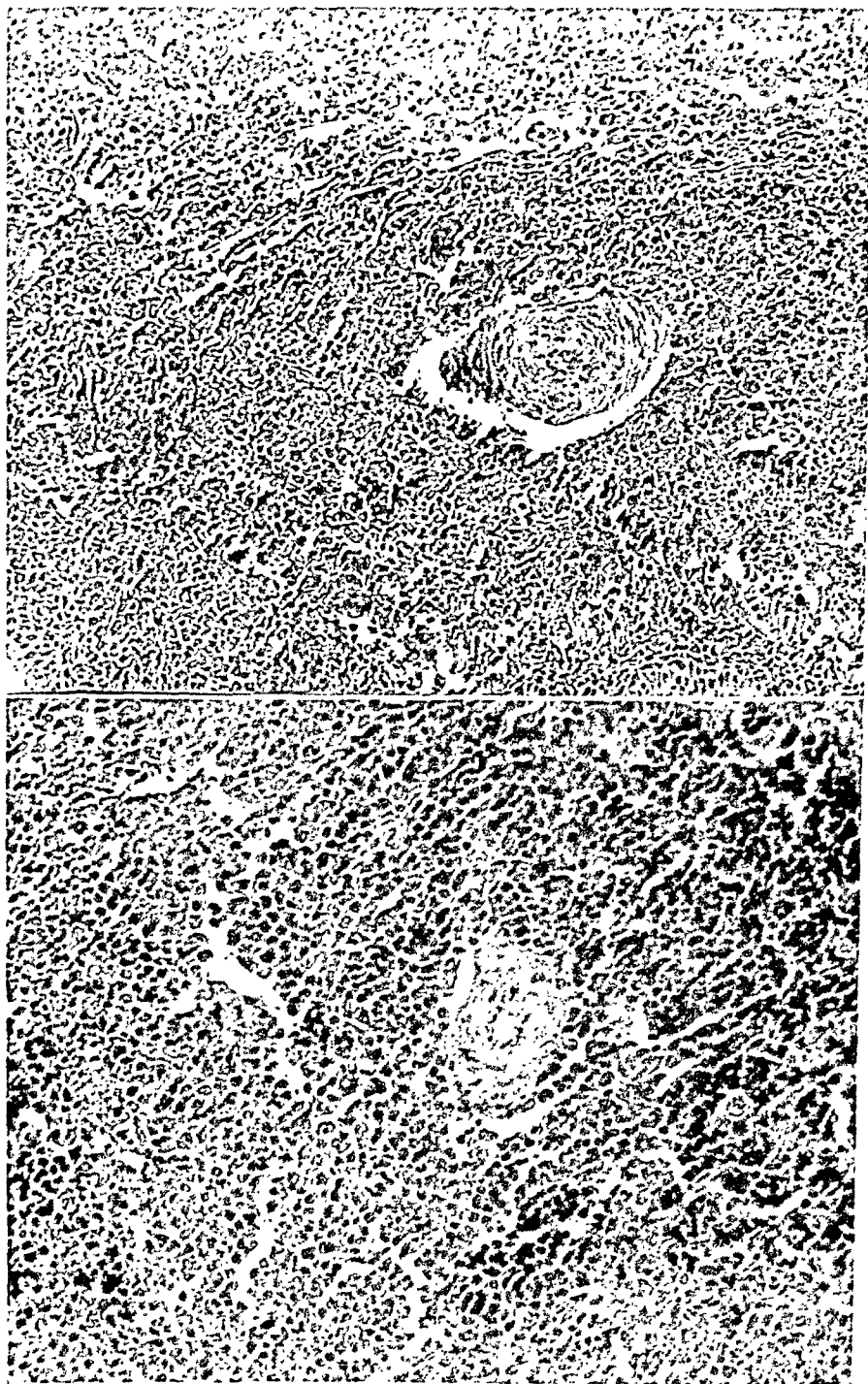


Fig. 3.—Spleen tissue obtained by biopsy from rat No. 8. Note the great thickening of the wall of the arteriole.

Fig. 4.—Pancreas tissue obtained by biopsy from rat No. 2. Note the great thickening of the wall of the arteriole.

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555 PROSPECT PLACE

Addendum

Since this manuscript was submitted for publication, an additional report on this subject has been published. Emil Novak (*J. Mount Sinai Hosp.* 14: 529, 1947) describes one case of this type.

THE IMMEDIATE POSTPARTUM PERIOD AS A FOURTH STAGE OF LABOR

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THE immediate postpartum period is defined as that interval after the expression of the placenta unto complete reaction of the patient to the delivery, including a satisfactory contraction of the uterus without excessive bleeding. It is difficult to state precisely when labor begins and when it ends. However, no significant puerperal changes occur until the patient has reacted to the delivery.

The duration of the immediate postpartum period, hereafter also referred to as the fourth stage of labor, will vary from the traditional hour in the average normal patient to many hours if abnormal events occur (see case reports).

Can the immediate postpartum period be properly regarded as a stage of labor? It has distinct clinical, anatomic, physiologic, and pathologic characteristics which are a denouement or anticlimax to the other three stages. The inclusion of this period in the definition of labor seems justifiable, although it is customary to consider it as the beginning of the puerperium.

Some authors, including Busey, King, and Jewett, have included this period in their definition of labor. They regarded labor as having ended when the uterus became firmly contracted. DeLee included the early regressive changes in the puerperium in his definition of labor. Stander states that the hour following delivery is just as important as the actual third stage, and that *these two periods* are more dangerous to the mother than the other stages of labor.

Modern obstetric practice includes certain procedures after delivery that modify the classical concept of labor. These practices were uncommon a hundred years ago when labor ended with delivery of the placenta. Today, obstetric anesthesia permits the immediate repair of lacerations and episiotomies after expression of the placenta. Oxytocics are given. On occasion, the uterus is explored and packed. These events take place in the delivery room as a part of the delivery and therefore of labor, and not of the puerperium. Furthermore, as the delivery is preceded by an antepartum period of uterine contractions and cervical dilatation, so it is followed by an immediate postpartum period of uterine contraction and cervical regression before actual involution begins. For these reasons, as well as the characteristics to be presented below, the immediate postpartum period easily comes within the definition of labor.

The following case reports were abstracted from the patients' records with the permission of the attending obstetricians in each instance. They illustrate the concept of the immediate postpartum period as the fourth stage of labor.

CASE 1.—Mrs. S. S., No. 434572, was a 28-year-old primigravida who had an operative (low forceps) delivery at term (3,800 Gm. infant). Analgesia was given including nembutal, scopolamine, and demerol. The delivery was performed under nitrous oxide, oxygen, and ether anesthesia. The duration of the first stage of labor was sixteen hours; the second stage lasted thirty-seven minutes; and the third stage, ten minutes. The placenta separated by the Duncan mechanism and was expressed from the vagina in the usual manner. The blood loss in the third stage was 400 c.c. Intramuscular pituitrin and ergotrate were given. After expression of the placenta, bleeding continued and ergotrate was given intravenously on three occasions. The uterus was also packed and a total of 4000 c.c. of blood was given. Oxygen was also administered. As a result of these measures the patient rallied and was sent to her room eight hours after delivery.

She regained partial consciousness. Oxygen was continued, as well as pantopon, penicillin, and other measures. Nevertheless, the patient died twenty-seven hours and thirty-three minutes after completion of the third stage of labor.

An autopsy was not obtained, but a postmortem exploration of the vagina and uterus revealed a small tear in the posterior fornix that communicated with the abdominal cavity.

The duration of the fourth stage in this case would be twenty-seven hours and thirty-three minutes. The patient never reacted completely to the delivery, and there was a pack in the uterus at the time of death, so that firm contraction was never observed.

CASE 2.—Mrs. G. G., No. 460184, was a 21-year-old primigravida, who was delivered spontaneously at term of a 3,650 Gm. infant. No analgesia was used in labor; nitrous oxide, oxygen, and ether were administered for the delivery. The duration of the first stage of labor was five hours; the second, two hours and two minutes; and the third stage, four minutes.

The placenta was expressed in the Schultze mechanism, with a blood loss of 150 c.c. Routine pituitrin and ergotrate were given intramuscularly, and the fundus was held for one hour. Thereafter, the patient was returned to her room in good condition, having reacted completely to the anesthetic.

Four and one-half hours after delivery the patient passed some membranes and 250 c.c. of blood clots. A second dose of ergotrate was given. Seven hours after delivery an additional 800 c.c. in blood clots was expressed from the uterus, and thereafter the fundus remained firm, and no further bleeding occurred. A transfusion of 500 c.c. was given which was repeated in several days because the red count was still low.

The duration of the fourth stage of labor in this patient was seven hours (and not one hour as originally recorded in the labor room), counting from the time the placenta was expressed until the uterus remained firm with no excessive bleeding.

CASE 3.—Mrs. A. D., No. 281078, para i, gravida ii, was delivered spontaneously at term of a 3,500 Gm. infant after a precipitate labor. The duration of the first stage was eight hours; the second, fifteen minutes; and the third, four minutes. The total blood loss was 30 c.c. No analgesia or anesthetic was required. The uterus was held for an hour after delivery, and it remained firm.

This patient had a fourth stage of an hour's duration, the conventional period of time for holding the fundus. Most obstetric cases will fall into this category.

Historical

Leishman (1875) credits Desormeaux (1778 to 1830) with the time-honored classification of labor into three stages. Desormeaux was the successor to Baudeloque at the University of Paris in 1811. There is some precedent for dividing labor into four stages. Samuel Bard (1808) did so in the first American textbook published in America. He considered the third and fourth stages as the expulsive and placental periods. Smith (1858) in England and Edgar (1907) in America both described a preliminary or preparatory stage in addition to the classical description. Milne (1884) said that, while some authors taught four and even five stages, he preferred to use three. All modern textbooks divide labor into three stages.

Madame Bourgeois (1609), the first midwife to write an obstetric textbook, limits the immediate postpartum period to one or two hours, and describes its management as follows: "As soon as the woman is delivered after a hard labor, she must be put in the skin of a black sheep which has been flayed alive. This is applied to the back. To the belly is applied the skin of a hare which has also been flayed alive. . . . This chases away melancholic blood. In winter these remedies must be kept on two hours and in summer one hour." Chapman agreed with this!

DeLee (1913), stated that the accoucher should remain in the house for an hour, and before leaving should assure himself on the following seven points: i.e., uterus, hemorrhage, placenta, bladder, tears, infant, patient.

Stander (1936), in addition to the statement referred to above, also said that the hour following delivery was just as important as the actual third stage from a practical point of view.

Morris Leff (1939) defined and described the management of the third and fourth stages of labor, the latter constituting the immediate postpartum period. Leff considered the fourth stage at an end when the patient had been returned to her room. This extent of time is insufficient as shown by Case 1. The same author (1945) described the effect of oxytocies on the physiologic picture of the third and fourth stages. Greenberg (1946) gave his views on the physiology of the contractile and hemorrhagic phases of a fourth stage, which was limited to the first postplacental hour. This period of time is sufficient for the average case (see Case 3) but not for abnormal cases as described in Cases 1 and 2.

The present article is a presentation of a definition of the immediate postpartum period, and a description of its clinical, anatomic, physiologic, and pathologic characteristics.

Discussion

The prevailing concepts of the immediate postpartum period need no revision in order to include it as a part of the process of labor. One need only to reflect on the clinical, anatomic, physiologic, and pathologic characteristics of the immediate puerperium to realize that this period is truly a stage of labor.

The *clinical* aspects of this period include the following: effects from analgesia or anesthesia; estimating or measuring the blood loss; postpartum administration of oxytocies; repairing lacerations or episiotomy; holding the fundus for an hour after delivery; checking the pulse, respirations and blood pressure; examining the placenta; caring for the infant (tying the cord, silver nitrate, weight, etc.); sometimes removing membranes or a succenturiate lobe;

exploring the uterus or packing it; transfusions; etc. When the patient has completely recovered from the effects of labor and delivery, including analgesia and anesthesia used in labor, with the uterus remaining firmly contracted without excessive bleeding, the fourth stage of labor may be considered clinically at an end.

The *anatomic* characteristics include the firm, thick fundus or the active segment of the uterus, and the thinner, loosely contracted lower uterine segment and cervix, or passive segment. The placental site consists of compressed uterine glands in the basal layer (Gebhardt's glands), which are invaded by chorionic giant cells according to J. W. Williams, whose article on the subject was published posthumously in 1931. He stated that it was often impossible to detect the placental site grossly in fixed specimens removed after cesarean section.

Physiologic characteristics include the alternate contraction and relaxation of the uterus after completion of the third stage. The placenta has separated along Nitabuch's layer between the placenta and the decidua vera. Festooning and shortening of the uterine muscle fibers reduce the size of the uterus as well as the placental site. Bleeding may continue after the placenta has been expressed. Extreme relaxation or uterine atony at this time may result in postpartum hemorrhage and death, as shown in Table I.

The *pathologic* aspects of the immediate postpartum period constitute important complications. These include: retained membranes, cotyledons, or succenturiate lobes; rupture or inversion of the uterus; vaginal lacerations; postpartum chill; postpartum hemorrhage; convulsions of eclampsia; cardiorespiratory failure; drug or anesthetic reactions, and aspiration pneumonia.

The various causes of maternal death occurring in the immediate postpartum period serve to make this stage of labor doubly significant. A total of 88 maternal deaths occurring at the New York Lying-In Hospital from 1932 to 1945, includes 28 patients (32 per cent) who died during the immediate postpartum period of labor. The causes of death in these patients are given in Table I. Lafferty has reported that 33 per cent of the maternal deaths in Philadelphia occurred within the first twenty-four hours of delivery.

TABLE I. CAUSES OF DEATH IN THE IMMEDIATE POSTPARTUM PERIOD OF LABOR

| | |
|--------------------------|----|
| Postpartum hemorrhage | 12 |
| Cerebrovascular accident | 5 |
| Cardiac failure | 4 |
| Anesthesia | 2 |
| Aspiration pneumonia | 2 |
| Rupture of uterus | 2 |
| Transfusion reaction | 1 |
| Total | 28 |

Summary

Definition.—The immediate postpartum period may be defined as the interval after expression of the placenta to a satisfactory reaction of the patient to the delivery, including a firmly contracted uterus without excessive bleeding.

The duration will vary from the traditional hour, under normal conditions, to many hours when abnormal conditions arise. Ordinarily, the period will be of sixty minutes' duration, the conventional interval of time for holding the fundus. The concept was illustrated with case reports.

This period has definite clinical, anatomic, physiologic, and pathologic characteristics that justifies its inclusion in the definition of labor as a separate fourth stage. These characteristics are the anticlimax to the preceding three stages of labor.

Twenty-eight, or one-third of a total number of eighty-eight maternal deaths occurred, or were recognized, in the immediate postpartum period. The commonest cause was postpartum hemorrhage. Emphasis should be placed on this stage by recording its events as part of the labor history.

The characteristics of the immediate postpartum period as a stage of labor should be publicized nationally. It is expected that such a program will serve to reduce the number of preventable maternal deaths occurring during the fourth stage of labor.

The exact definition and connotation of the immediate postpartum period as a fourth stage of labor will depend on additional observations and recorded reports, as was the case with the other three stages. Meanwhile, there need be no doubt that this period is truly a part of labor.

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PREMATURE QUADRUPLETS

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THE quadruplets whose birth is reported here are the children of Mr. and Mrs. C. H., Jr., of Baltimore, Maryland. The father is an American of English ancestry, born in 1920, and the mother an Englishwoman, also born in 1920, who came to the United States as a war bride. There is no history of multiple births on either side of the family. The couple have an older child, a boy $1\frac{1}{2}$ years of age at the time of the birth of the quadruplets. This previous pregnancy ran a normal course, and the child has grown and developed normally.

On July 20, 1946, when the patient was two months pregnant (with quadruplets, as was afterwards ascertained), she had an attack of acute appendicitis. A gangrenous appendix was removed through a McBurney's incision. The ovaries could not be seen. Recovery was rapid and uneventful.

When the patient first presented herself to the obstetrician (Bowyer) on September 3 for prenatal care, she had no complaints as to health and was at or near her normal weight of 135 pounds. She was Rh positive. The last menstrual period having begun May 2, 1946, the calculated date of delivery was Feb. 9, 1947. Nothing unusual was found on physical examination except that the fundus uteri was 20 centimeters above the symphysis pubis. This finding indicated that delivery would occur about Dec. 9, 1946, rather than in February, 1947, but at the time it was assumed that the patient had erred about the menstrual history.

The next prenatal visit was on Oct. 4, 1946. There were no complaints. The patient now weighed 153 pounds. The blood pressure was 124/72. There was no albumin in the urine. The height of the fundus uteri was 24 centimeters. Fetal heartbeats were not heard, but the patient stated that she felt slight fetal movements.

On Nov. 11, 1946, there were still no complaints. The blood pressure had risen to 145/88. The weight was 165 pounds, having increased 12 pounds since the previous visit. Edema of the whole body was noted. The urine showed specific gravity of 1.028, no albumin. Two fetal hearts were heard.

The patient was put to bed for one week at home with a diet of milk and sweetened fruit juices, and was given $\frac{1}{2}$ oz. of magnesium sulfate daily. At the end of the week her blood pressure had dropped to 130/70; the weight had decreased 3 pounds during the week, to 162 pounds. The urine remained free of albumin; the specific gravity was 1.016.

At this time, i.e., November 18, two hundred days after the last menstrual period, an x-ray examination was made by Dr. Eugene L. Flippin, which clearly revealed a quadruple pregnancy (Fig. 1): In view of this finding, complicated with a mild pre-eclamptic condition, immediate hospitalization was advised for the duration of the pregnancy and the patient was moved to St. Agnes Hospital.

At the time of entering the hospital, Nov. 20 1946, the patient had a blood pressure of 130/80. The weight was 162 pounds. The urine was normal. Treatment consisted of a simple low caloric diet with unlimited tea. The weight,

blood pressure, intake and output of fluids, and urinary findings were recorded daily, and showed no significant changes, remaining within the range of normal single pregnancy. On December 22 the weight was 166 pounds, blood pressure 122/72.



Fig. 1.—Radiograph of pelvis showing four fetal heads. The outlines of the heads have been slightly strengthened by retouching in order to make them visible in the half-tone reproduction (reduced).

At 1:00 A.M. on December 23 the patient complained of mild indigestion, which persisted for seventeen hours. Repeated rectal examinations during this time failed to reveal a presenting part, although there was a slow dilatation of the cervix with bulging of the membranes through the cervical canal. The contractions could not be timed. At 6:30 P.M. the patient said something was hanging from her vagina. This proved to be an intact amniotic sac. She was

Fig. 2.

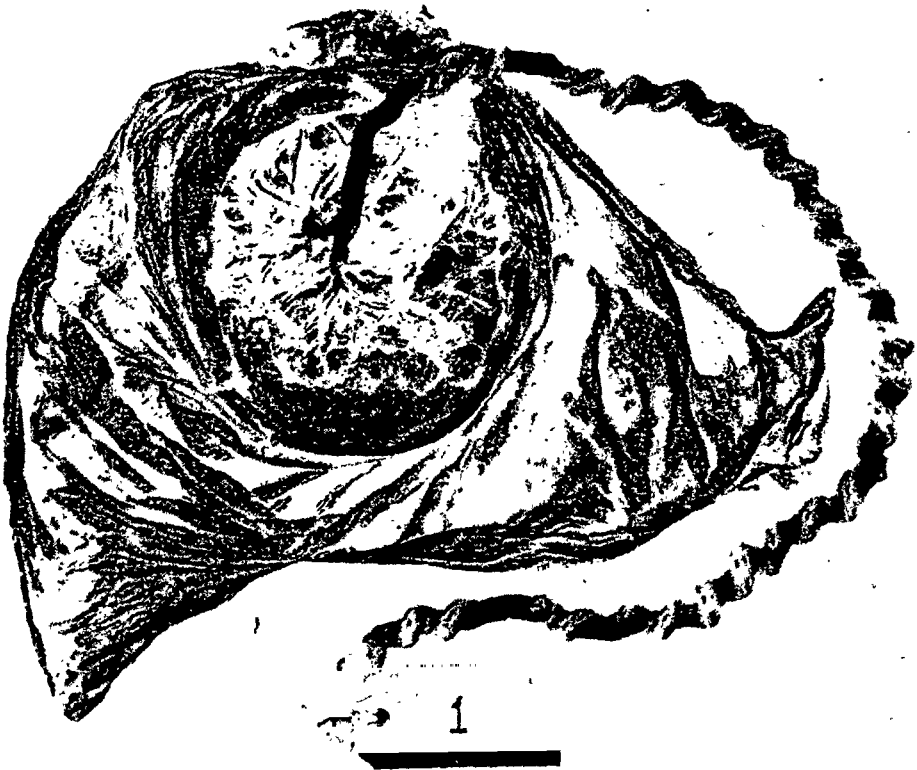


Fig. 3.

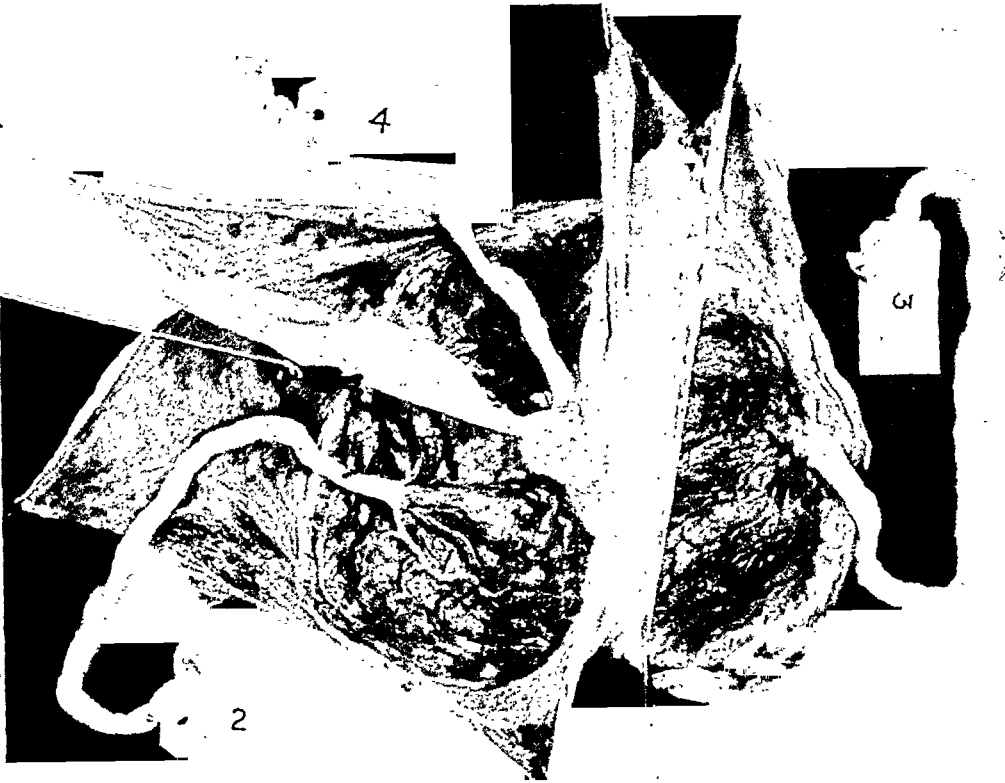


Fig. 2.—Placenta (No. 1) of infant A.

Fig. 3.—Fused placentas and membranes of infants B (2), C (3), and D (4).

moved to the delivery room, the amniotic sac was artificially ruptured, and in five minutes the first baby was born. Spinal anesthesia was to have been employed, but because of the rapidity of events, it was not administered and the labor was completed with no anesthetic and without serious pain. Delivery took place in the following order, and was spontaneous except that in each case the amniotic sac was artificially ruptured.

- A. Left occipitoanterior, male, 6:45 P.M. The corresponding placenta was delivered at 6:50 P.M.
- B. Left occipitoanterior, male; 7:04 P.M.
- C. Right sacroanterior, male, 7:34 P.M.
- D. Right occipitoanterior, female, 7:40 P.M.

The three placentas of the three last-born infants were delivered as a fused mass at 7:45 P.M.

The four infants were marked, as usual, with identification tags, and each cord, as soon as it presented itself, was tagged with a number, 1, 2, 3, and 4, corresponding respectively to infants A, B, C, and D. This precaution would have been essential for subsequent embryologic and anthropometric studies, had the case turned out to be one of mixed single-ovum and multiple-ovum gestation.

The patient remained in the hospital sixteen days after parturition. Her convalescence was uneventful in every respect and she was walking about in ten days.

The weight of the infants at birth was A, 1,320 Gm.; B, 1,740 Gm.; C, 1,920 Gm.; D, 1,590 Gm. The children have thrived under pediatric care with the usual care and feeding given premature babies. At the end of April, 1947, four months after birth, they were all well and each weighed in excess of 11 pounds (5,000 Gm.).

Description of the Placentas and Membranes

The placentas and membranes were given to the embryologist (Corner) about one half hour after delivery. These specimens, with the records and photographs, are filed in the Carnegie Embryological Collection under the serial number 8448. The placenta of infant A, which was delivered immediately after the infant, and before the birth of infant B, measured 14 by 13 cm. It weighed, after several days in 10 per cent formalin, 477 Gm., and must therefore have weighed about 455 Gm. in the fresh state. This placenta was eccentrically circumvallate, i.e., at one side (seen at the top of Fig. 2); the membranes were attached about 3.5 cm. inside the margin of the placental tissue, whereas at the other side they were attached to the placental border. The "vallation" or elevation of the extra-chorionic zone of the placenta was not over two millimeters above the level of the placenta within the membranes.

Placentas 2, 3, 4, and the corresponding membranes were firmly fused to each other, as seen in Fig. 3. When examined fresh at the laboratory it was erroneously thought that the septum between sacs 2 and 4 was thinner than the others, and that the chorion was possibly continuous over the line of fusion of the amnions. Indiscreet mention of this possibility to a reporter led to inaccurate newspaper reports which were widely circulated. It was thought best not to investigate the fused membranes for fear of tearing them. The three sacs were therefore packed lightly with cotton, to keep them distended, and the whole mass was placed in 10 per cent formol.

After fixation it was clearly apparent that there were three separate chorions, which were firmly affixed but could be separated by pulling them apart.

TABLE II. BLOOD PRESSURE

| RATS | FIRST WEEK | SECOND WEEK | THIRD WEEK |
|------|------------|-------------|------------|
| 1 | 145/150 | 145/145 | 170/175 |
| 2 | 160/160 | 165/160 | 185/180 |
| 3 | 140/140 | 145/140 | 140/140 |
| 4 | 110/115 | 120/125 | 125/120 |
| 6 | 170/165 | 160/160 | 175/160 |
| 7 | 110/130 | 155/150 | 160/165 |
| 8 | 150/155 | 160/150 | 150/155 |
| 10 | 135/140 | 140/140 | 160/165 |

Two rats had ascites which was proved by paracentesis. One rat had convulsions on two occasions while being heated in the electric cradle. No other abnormal symptoms were observed. All rats carried their pregnancies to term. Six of them had their litters born normally, while the other two had stillborn pups.

Pathology.—Biopsies were taken from the kidneys, spleen, pancreas and liver of all these rats. Sections showed one striking consistent result, i.e., arterio-sclerosis. Some glomerular tufts were ischemic and the basement membranes thickened. (See Figs. 1, 3, and 4.)

Conclusion

A condition closely simulating toxemia of pregnancy with albuminuria, hypertension and edema was produced in rats by sensitizing them against placenta protein before they became pregnant. The most important pathological lesions were found in the arterioles. The walls became greatly thickened and the vascular lumen correspondingly narrowed. There was in the kidney some thickening of the basement membrane of Bowman's capsules as well as ischemia of the glomerular tufts. This pathology corresponds closely to the early lesions in the human toxemia of pregnancy. Wong and Pillot¹⁵ has reported that the earliest sign of toxemia of pregnancy is spasm of the arteriolar wall and the narrowing of its lumen which can be observed in the eye grounds.

The findings in this preliminary experiment suggests that toxemia of pregnancy might be an allergic reaction of the patients to the placental proteins.

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NONFATAL PULMONARY EMBOLISM BY AMNIOTIC FLUID CONTENTS WITH REPORT OF A POSSIBLE CASE*

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STEINER and Lushbaugh,¹ in October, 1941, presented a syndrome entitled "Maternal Pulmonary Embolism by Amniotic Fluid" as one cause of unexplained shock and unexpected death in obstetrics. In their original monograph they demonstrated the presence of emboli in the lungs of obstetric patients at autopsy, the emboli being due to particulate matter contained in the amniotic fluid. These authors then produced experimentally a similar clinicopathologic picture in dogs and rabbits by the intravenous injection of suspensions of particulate matter obtained from amniotic fluid. Their original paper¹ gave the clinical histories and pathologic findings in eight human patients; a later publication² by the same authors added two more cases to their series. All ten cases ended fatally, the diagnosis being made only at autopsy. During the preparation of this paper a case report appeared in the February, 1947, issue of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY by Hemmings,³ adding to the literature the eleventh case of fatal maternal embolism from amniotic fluid contents, proved by autopsy findings. To date no case report can be found in which the *clinical* diagnosis of this syndrome had been made either preceding or following the death of the patient, in all instances it seems to have been an unexpected finding at necropsy. Furthermore, we have been unable to find a single recorded instance of recovery of a patient suspected to have had this type of embolus.

A young woman who went into profound shock during parturition was recently delivered on the obstetric service of the Sinai Hospital. Her clinical course, physical findings, and roentgenologic evidence strongly suggest that her case may be an instance of pulmonary embolism by amniotic fluid contents which *did not* end fatally. The case history follows.

Case Report

Mrs. M. L. A., an 18-year-old white primigravida, registered in the prenatal clinic on May 5, 1946. Her past history was negative, except for pneumonia at the age of four years. There was no history of previous rheumatic fever or heart disease. Expected date of confinement was Jan. 12, 1947. Physical examination at registration revealed systolic murmurs at both the apex and base, which were not transmitted and considered to be functional. Blood pressure was 128/62; height, 62 inches; weight, 102½ pounds (nonpregnant 99 pounds); blood: S.T.S. negative, Group O, Rh positive. X-ray of chest on May 13, 1946, revealed: "Heart is average size and shape. Diaphragms regular. Lung fields are clear."

*Presented at a meeting of the Baltimore Obstetrical and Gynecological Society March 14, 1947.

The three placentas were fused to such an extent that they could not be separated without tearing placental tissue, although three separate masses were more or less clearly demarcated by depressions on the maternal surface.

The following measurements and characteristics of the placental components were noted:

The total weight, after several days in formol, was 1,385 Gm. The weight when fresh must have been about 1,320 Gm., or slightly more than three times the weight of the single placenta corresponding to infant A. The dimensions were:

No. 2, 18 by 11.5 cm., cord slightly eccentric;

No. 3, 17 by 11 cm., cord very eccentric, attached near margin of the placental mass;

No. 4, 15 by 11.5 cm., cord very eccentric, attached near center of the placental mass.

These findings indicate that the four infants developed from four separate fertilized ova and that three of them (B, C, D) became implanted so closely together that their placentas began to fuse, and hence to modify each other's form, relatively early in pregnancy.

Summary

A case of fraternal quadruplets, three boys and one girl, diagnosed by x-ray at two hundred days (menstrual age) and born prematurely at 235 days.

found to be hardly obtainable, rapid and thready. Blood pressure could not be obtained. Respirations were rapid, shallow, and labored. Immediate auscultation of the chest revealed both lung fields to be filled from apices to bases with coarse, moist, bubbling râles, so loud as to almost obscure the very rapid heart sounds. This occurred at 10:30 P.M., eighteen minutes post delivery.

Anesthesia was immediately stopped, 100 per cent oxygen given, patient's position changed to reverse Trendelenburg, and cardiac stimulants were ordered. Medications given were 1 ampule of digalin intramuscularly at 10:40 P.M.; 1 ampule of adrenalin intramuscularly at 10:42 P.M., $\frac{1}{150}$ grain of atropine intravenously at 10:45 P.M. The patient was still deeply cyanotic, both skin and nails, dyspneic in spite of constant oxygen, and respirations were rapid and shallow. The diagnosis of pulmonary embolus due to meconium was ventured at this time by an attending obstetrician (W. S.) who was present. Intravenous fluids were interdicted for the time being.

From this point treatment of the patient was continued with the cooperation of the medical resident staff. Tourniquets were placed on three limbs, and alternated every twenty to twenty-five minutes. Cedilanid, 4 c.c. intravenously, was given at 11 P.M. Caffeine-sodium-benzoate, 2 c.c. intramuscularly, was given at 11:10 P.M. Pulse and blood pressure were still unobtainable. Auscultation of the heart was unsatisfactory due to the loud inspiratory and expiratory moist bubbling pulmonic râles.

For a short time the left chest cleared of râles somewhat and the apex rate was found to be 144 per minute, with definite gallop rhythm. An electrocardiogram taken at about 11:15 P.M. showed sinus tachycardia. Morphine sulfate, $\frac{1}{6}$ grain, and atropine, $\frac{1}{150}$ grain, were given intramuscularly at 11:30 P.M.

At 12:15 A.M., two hours post partum, blood pressure was obtainable for the first time and was 96/80. At about 12:30 A.M. a whole citrated blood transfusion was started at approximately 25 to 30 drops per minute. Cardiac rate at this time was 140 to 150. Morphine, $\frac{1}{6}$ grain, and atropine, $\frac{1}{150}$ grain, were given intramuscularly at 1:10 A.M. Penicillin, 60,000 units, were given every three hours. Patient was still in poor condition, with extreme cyanosis and polypnea.

At 3:00 A.M., five hours post partum, the patient was considerably improved. Gallop rhythm was still present, with a rate of 150. Two cubic centimeters of cedilanid were given intramuscularly. Patient was still getting 100 per cent oxygen on the table.

At 4:00 A.M., six hours post partum, the patient's temperature was 101° F.; pulse 120; respirations 34. Blood transfusion was completed.

At 9:00 A.M., eleven hours post partum, the patient's temperature was 100° F.; pulse 130; respirations 32. The patient was in an oxygen tent and receiving oxygen through a nasal catheter. She was very cyanotic, moderately dyspneic, and apprehensive. Both lungs filled with bubbling moist râles again, and she was coughing up frothy, watery, blood-tinged sputum. Tourniquets again were applied to limbs and 2 c.c. cedilanid were given intramuscularly.

Portable chest film showed that the heart did not appear to be enlarged. Mediastinum was not shifted. The intercostal spaces were equal bilaterally. Diaphragms were in normal position. There was an area of increased density involving the second and third anterior interspaces on the left side, and also involving the lower two-thirds of the right lung, more marked at the base of the seventh rib posteriorly. From the shape of these dense areas, infarctions could not be ruled out (Fig. 1).

At 10:30 A.M., twelve and one-half hours post partum, 300 mg. of dicoumarol by mouth and 50 mg. of heparin were placed in 500 c.c. of normal saline

Patient was seen regularly; and her course was uneventful. She had no cardiac signs or symptoms, and it was not deemed necessary to send her to the Obstetric-cardiac clinic for investigation of her murmurs. On Dec. 10, 1946, the fetus was in breech presentation, and she was seen at weekly intervals thereafter. X-ray pelvimetry on Jan. 7, 1947, revealed: Single fetus, breech presentation. Obstetrical conjugate 11.4 cm. Transverse of inlet 13.0 cm. Bispinous 11.2 cm. Bituberous 11.2 cm. Adequate gynecoid pelvis." She was seen in the prenatal clinic on Jan. 28, 1947, the fetus still in breech presentation, cervix soft, thick, and 2 cm. dilated. Blood pressure was 170/100 and weight 117 pounds, a gain of 3 pounds in one week, and a total gain of 18 pounds during pregnancy. Urine was negative. Because of rise in blood pressure, sudden gain in weight, three weeks postmaturity, engagement of the presenting part at the spines, and favorable cervix, admission for induction was advised.

She was admitted at 8:15 A.M. Jan 29, 1947, not in labor, with a blood pressure of 140/80. A routine medical induction with 1 ounce castor oil, a soapsuds enema, and pitocin was given. The latter was started at 9:15 A.M. on January 29, receiving $\frac{1}{2}$ minim of pitocin for two doses and 1 minim for four doses, each injection given intramuscularly at twenty-minute intervals. Irregular uterine contractions began at 11 A.M. Pitocin was completed at 12:05 P.M. Uterine contractions became regular at 1:00 P.M., occurring every five to seven minutes. Labor progressed slowly although contractions were good, and 50 mg. of demerol and grain $\frac{1}{150}$ of scopolamine intravenously were given at 6:30 P.M. Scopolamine, $\frac{1}{150}$ grain intramuscularly, was repeated at 7:30 P.M. At 4:30 P.M. blood pressure was 190/100, and at 5:30 P.M. 160/100.

At 7:30 P.M. the cervix was fully dilated, fetus was presenting as a frank breech in right sacroposterior position. First stage lasted eight hours and thirty minutes.

She continued in the second stage of labor for two hours, when the breech reached the perineum and the membranes were artificially ruptured. The contents of the amniotic sac consisted entirely of undiluted meconium.

Nitrous oxide and oxygen anesthesia was started at 9:55 P.M., and the anesthetist noted that adequate anesthesia could be maintained with a minimal amount of nitrous oxide, so that at times the patient received practically pure oxygen. In spite of this, moderate cyanosis was noted by the anesthetist periodically throughout the delivery and repair.

Delivery was preceded by a deep left mediolateral episiotomy. Strong suprapubic pressure was made by the assistant (W. S.) until the operator (L. M. S.) could reach the anterior groin with an index finger. By moderate traction the breech was delivered without great difficulty. The body, arms, and shoulders followed in the usual manner. Piper forceps were applied to the aftercoming head to complete the delivery. The 6 pound 3 ounce male child was born at 10:10 P.M. Jan. 29, 1947. The second stage of labor lasted two hours and forty minutes. Ergotrate, 1 ampule, was given intravenously at 10:10 P.M., and 1 ampule of pitocin intravenously at 10:16 P.M. The placenta and membranes were expressed intact at 10:12 P.M., and it was noted that the membranes and amniotic surface of the placenta were stained a deep meconium green. The third stage lasted two minutes. Total labor eleven hours twelve minutes. Blood loss was estimated to be 150 cubic centimeters.

The baby appeared to be in good condition, but initial respiration and crying were slightly delayed—being two minutes fifty seconds; and four minutes thirty seconds, respectively.

Toward the end of the episiotomy repair it was noted that the blood oozing from the perineum was quite dark, and further inspection revealed mixed pallor and cyanosis of the face, and marked cyanosis of the fingernails. The pulse was

in the right apex. Many fine moist râles were present. No cough or sputum was noted. Color was good, but the patient was still in the oxygen tent and receiving oxygen through a nasal catheter. The abdomen was soft, and the liver and spleen were not palpable. Extremities were negative for any evidence of phlebitis.

Fourth Postpartum Day.—The patient was removed from the oxygen tent without return of cyanosis. She was not coughing or bringing up sputum. Temperature had been normal for two days.

Fifth Postpartum Day.—Chest x-ray showed that a comparison with the film of Jan. 30, 1947, revealed that the extensive areas of infiltration in both lung fields had completely resolved. This would indicate that the original pathologic process was pulmonary infarction. Approximately ninety-six hours had lapsed between films (Fig. 2).

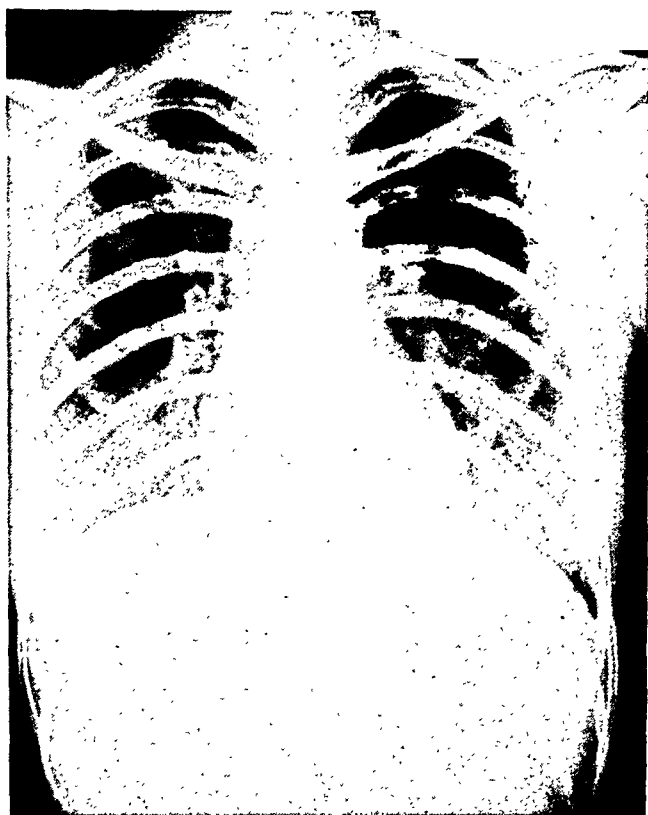


Fig. 2.—X-ray of chest ninety-six hours post partum.

The remainder of her hospitalization was marked by progressive improvement, and was complicated only by the development of an area of moderate pain in the left anterior axillary line at the costal margin. The latter was aggravated by deep inspiration, no cough, and gradually disappeared after three days. She was allowed out of bed on the eighth postpartum day, and was discharged on February 13, 1947, fifteen days after delivery, apparently fully recovered. She was followed up on two successive visits to the hospital at two- and six-week intervals; physical examination at these visits was completely negative, and she presented no complaints.

Discussion

It is to be noted at once that our case differs radically from those previously reported, since they were uniformly fatal. However, the existence of

solution and started by slow intravenous drip. Hematology; red blood cells, 5,250,000; hemoglobin, 16.2 Gm. (112 per cent); white blood cells, 15,000; polymorphonuclears, 93 per cent; lymphs, 7 per cent; sedimentation rate, 32.

At 2:00 P.M., sixteen hours post partum, the blood pressure was 98/80. Temperature 101° F., pulse 124, respirations 52.

At 10:00 P.M., twenty-four hours post partum, the patient took a sudden turn for the worse and became deeply cyanotic, dyspneic, and anxious. Respirations were 64; her pulse was regular, and she had an equal cardiac rate of 134. Her blood pressure was 120/100. A marked gallop rhythm was still present. Chest signs were noted as above, with scattered râles. She was raising small amounts of thin, pink, frothy sputum. Morphine, $\frac{1}{4}$ grain, and atropine, $\frac{1}{150}$ grain, were given intramuscularly, and the patient responded promptly. She fell asleep, her respirations dropped slightly, and the dyspnea decreased.



Fig. 1.—Portable chest film twelve hours post partum.

Second Postpartum Day.—At 9:00 A.M., thirty-five hours post partum, a remarkable improvement was noted in patient's condition. Her temperature was 101.2° F.; pulse was 104 and regular; respirations were 40. Gallop rhythm had disappeared. Her left chest was clear of râles. Breath sounds at right apex were still tubular. White blood cells were 12,700; polymorphonuclears, 89 per cent; lymphs, 9 per cent; monocytes were 2 per cent.

At 12:30 P.M., thirty-eight and one-half hours post partum, the patient had received a total of 200 mg. of heparin and 300 mg. of dicoumarol in twenty-four hours. Coagulation time was fourteen minutes, and prothrombin time 60 per cent of normal. Heparin and dicoumarol were discontinued.

Third Postpartum Day.—At 9:00 A.M., seventy hours post partum, the patient's temperature was normal; heart sounds were good; no gallop was present. Pulse was 90 and regular, respirations 30. Tubular breathing was less marked

to her recovery. Steiner,⁵ in a personal communication, suggests that being under general anesthesia when embolization probably occurred may have abolished enough reflexes in the acute stage to tide her over.

Diagnosis

Since this condition has never been diagnosed before death and autopsy, there are no *clinical* criteria for its recognition in the living patient. In our case, the sudden profound shock could have been due to any one of several causes. However, the combination of dyspnea, cyanosis, and marked pulmonary edema without cardiac disease suggested a sudden pulmonary complication. Some form of embolism seemed to be the logical explanation, and that of amniotic material, while somewhat dramatic and unusual, was thought of in the absence of any other apparent cause.

Pulmonary edema was an almost constant finding in Steiner and Lushbaugh's series of autopsied patients, as well as in their experimental animals, including those animals which survived embolization and which were subsequently sacrificed for pathologic study. In this latter group they found it very difficult to identify particulate matter in the lungs seven days after embolization, and they concluded from this that the subsequent fate of this material is probably complete removal.

In view of this experimental work we believe that the diagnosis in our case is fortified by the roentgenologic evidence of almost complete clearing of the lung fields in approximately 96 hours.

The clinical picture in the absence of known previously existing heart or pulmonary disease, the roentgenologic findings, and clinical course, follow rather closely the diagnostic and experimental criteria suggested by Steiner and Lushbaugh.

Differential Diagnosis

We realize full well that in suggesting pulmonary embolism from amniotic fluid as the etiologic factor in this case we invite skepticism by some. Without definite microscopic evidence to prove our thesis this skepticism may be valid. Of the other likely diagnoses we shall consider and discuss the following:

1. *Postpartum hemorrhage*: Blood loss was estimated at 150 cubic centimeters. This cause can be immediately dismissed.

2. *Pulmonary embolism from vascular thrombi*: This was strongly entertained as evidenced by the therapy given, however, she had no known previous heart disease and none was demonstrated subsequently. The patient was closely examined and watched for the presence of thrombophlebitis in the pelvis and lower extremities, but this did not develop. The rapidity of clearing of the lungs as demonstrated by x-ray, the failure of more embolism to occur, and the rapid recovery of the patient, all seem to speak against the diagnosis of vascular embolism. Furthermore, embolism from vascular thrombi *usually* occurs later in the puerperium.

3. *"Eclampsia without convulsions"*: In January, 1937, Teel, Reid, and Hertig⁶ described a symptom complex of cardiac asthma associated with acute

sublethal and even subclinical forms of this condition was suggested by Steiner and Lushbaugh.² To quote: "It is impossible to state the true incidence of this condition at the present time because the sublethal and even subclinical forms which *undoubtedly exist* have not been recognized." They estimate the fatal incidence of this complication to be 1 in 8,000 obstetric cases from the material obtained from the Chicago Lying-in Hospital. Analysis of 72 obstetric deaths by Steiner and Lushbaugh showed that pulmonary embolism by amniotic fluid contents was the *most common cause of death* in the period during labor and within the first nine hours thereafter. "Instead of being considered a rarity among serious obstetric complications, this must be thought of as one of the commonest."¹

The outstanding physical findings common to Steiner and Lushbaugh's cases and our own are: (1) cyanosis, (2) dyspnea, (3) fall in blood pressure, and (4) râles (pulmonary edema).

On the basis of their few cases, Steiner and Lushbaugh listed certain factors predisposing to this form of embolism. These included: (1) age: average age 32 years. (2) Parity: multiparas. (3) Tone of the uterus: tetanic or stronger than usual. (4) Character of the amniotic fluid: meconium or blood or excess of particulate matter. (5) Size of the fetus: exceptionally large. (6) State of the fetus: intrauterine fetal death in 50 per cent. Our case conformed to only one of these, i.e., the presence of a large amount of meconium in the amniotic fluid. The absence of strong or tetanic uterine contractions may have been substituted for by the strong suprafundic pressure made by the assistant during delivery. Yet this type of pulmonary embolism in the absence of labor contractions (occurring in a case of elective cesarean section) was demonstrated by Steiner and Lushbaugh in their second paper.²

Steiner and Lushbaugh discussed anaphylactoid shock as the probable cause of death in some of their cases.¹ This, combined with postpartum hemorrhage or pulmonary edema, was probably sufficient to cause the fatal outcome. In our case, uterine hemorrhage was clearly absent; anaphylactoid shock was not apparent; but pulmonary edema was striking. The absence of hemorrhage and anaphylaxis may have been largely responsible for her recovery. The fact that she was a young primigravida in good physical condition, and that she was not exhausted by a long, hard labor, may have been other factors favoring her recovery.

Steiner and Lushbaugh pointed out the experimental work of de Takats and associates⁴ who showed that atropine reduces pulmonary vascular spasm by depressing reflexes initiated in the lungs which exert a depressant action on the heart, further embarrassing circulation through the lungs. In their own experiments they gave atropine to dogs before embolization by amniotic fluid-meconium mixture, which seemed to decrease the severity of the shock reaction if the embolizing dose was not too overwhelming. Fortunately, our patient received two doses of scopolamine (a member of the atropine series) for analgesia during the first stage, and also was given atropine at once upon recognition of the pulmonary edema. These apparently constituted another factor which led

condition of the patient; (c) the fact that she was under a general anesthetic during the embolizing episode; (d) the apparent rapid "absorption" or at least complete removal of the particulate matter from the lung fields as shown by x-ray.

4. The differential diagnoses admissible in this case were briefly discussed.

5. The case is presented to call attention to the possibility of recognizing this syndrome soon after its occurrence in order that proper therapy be started immediately to prevent a fatal termination.

6. The interdiction of intravenous fluids or the very slow administration of whole blood in the presence of acute pulmonary edema, atrophinization, morphine and oxygen are the important therapeutic measures. Withholding of intravenous fluids in the face of severe shock requires courage and exercise of clinical judgment.

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Addendum

Since this paper was submitted, three additional cases have been reported by P. Gross and E. F. Benz (*Surg., Gynec. & Obst.* 85: 315-320, 1947).

pulmonary edema as a complication of nonconvulsive toxemia of pregnancy. As in our case, their patients were suddenly seized with severe dyspnea, cyanosis, orthopnea, and acute pulmonary edema, none of them having a known history of chronic hypertension, organic heart disease, or nephritis. But there the similarity ends. Teel, Reid, and Hertig's cases had definite toxemia—complete with hypertension, edema, albuminuria, and associated symptoms—our patient did not, her hypertension was transitory. None of their cases developed the profound state of shock with fall of blood pressure to 0/0 as did our case at the very onset of her attack. And, most convincingly—cardiac asthma with acute pulmonary edema would not explain the x-ray findings in the lungs of our patient.

4. *Aspiration of blood or stomach contents:* Our patient was anesthetized with unusual ease, did not vomit, or even cough during induction or in the course of the anesthesia, and, as far as is possible to ascertain, did not aspirate stomach contents or blood. Once again this diagnosis would not explain the roentgenologic evidence found in the lungs. Atelectasis would be the more likely x-ray picture.

5. *Nitrous-oxide asphyxia:* In asphyxia due to nitrous oxide there is a depression of the respiratory center (Cushny⁷) without apparent pathology in the lungs themselves. Usually the respiratory rate is decreased, and, if there is a rise in respiratory rate, it occurs in the initial stage of the asphyxia and is promptly followed by marked slowing of respiration. In our case the respiratory rate was greatly accelerated throughout. At this point it should be re-emphasized that the gas-oxygen mixture contained a high percentage of oxygen according to the statement of the anesthetist, a member of the hospital professional anesthesia staff. The cyanosis which occurred intermittently during the delivery and repair seems best explained by the hypothesis that embolization, either by meconium or other particulate matter, occurred early in the course of delivery. Furthermore, if this had been a pure anesthetic phenomenon one would anticipate more rapid recovery. It is also impossible to explain the x-ray findings on an anesthetic basis.

Summary and Conclusions

1. We have presented the case of an 18-year-old primigravida who suddenly went into profound shock, developed acute pulmonary edema with cyanosis, and was in imminent danger of death immediately following the delivery of a living 6 pound 3 ounce frank breech.

2. The diagnosis of pulmonary embolic phenomena from particulate matter in amniotic fluid is suggested as the etiologic factor for the symptom complex which developed. We cannot didactically state that this is positively a case of amniotic particulate embolism, as there are no known means of making a positive clinical diagnosis in the living patient. However, we believe it presents the most likely explanation for the symptom complex that occurred. The literature contains no report of recovery of a patient from this syndrome.

3. The recovery of our patient may be explained by a series of fortuitous events: (a) early diagnosis and appropriate therapy; (b) excellent physical

FUNGICIDES FOR VAGINAL MONILIASIS

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ALTHOUGH a large number of chemicals have been studied for fungicidal qualities,¹⁻³ a stainless, nonirritating, efficient compound is yet to be discovered. These organisms belong to the medical monilia group, more recently called *Candida albicans* by Jordan and Burrows.⁴

These fungi are found frequently in the intestinal and vaginal cavities without symptoms or evidence of mycosis. Vaginal moniliasis occurs almost always during pregnancy. Exceptions are in patients in which common sugars are used as vehicles for vaginal trichomoniasis therapy, or in postmenopausal individuals on excessive estrogenic therapy. Vulvar mycosis is uncommon except in uncontrolled diabetic patients. These established facts leads to the conclusion that these organisms are opportunists. Woodruff and Hesselstine⁵ found the frequency of these fungi organisms in the vagina in pregnancy varied in unselected patients from 14 per cent in the outpatient clinic at the Chicago Lying-in Hospital to 41 per cent among Negro group at the "Stock Yards" dispensary.

The promise of chlorothymol, mercuric chloride, and mercuraphen was unfulfilled or irregular fungicidal action on the assorted test strains was observed.⁶ Gentian violet has been most widely used, but its bold staining features and unsuitable forms for self-administration, along with an occasional sensitization, was the major stimulus to find a better agent, such as element iodine.⁶ Element iodine has an established fungicidal potency but it has not been used because no satisfactory method of application had been worked out.

To arrange selfadministration between office visits tablets of potassium iodate and also potassium iodide were made. Kaolin was used as a diluent to slow up the reaction and give prolonged action of the iodine. The acid in the vagina completed the well-known chemical reaction liberating iodine. By supplying sufficient potassium iodine a dilute Lugol's solution was made in vivo. Moderately good but not ideal results occurred, for infrequently a mild iodine "burn" was found in the vaginal vault. The mild degree of burn was verified by the fact that the patients were free from symptoms. Even though cures were effected this preparation was not an ideal agent for these vaginal mycoses.

Because a patient reported symptomatic improvement of her vaginal mycosis following the use of a contraceptive jelly, it seemed pertinent to investigate the various ingredients of this jelly and also a few other new compounds for fungicidal potency against a medical monilia (No. 6225).

ERYTHROBLASTOSIS FETALIS DUE TO INTRAGROUP Rh INCOMPATIBILITY

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IT IS well recognized that erythroblastosis fetalis is caused by isoimmunization of an Rh-negative mother by the Rh-positive cells of her fetus in 90 per cent of the cases.¹ In the remaining 10 per cent this syndrome is produced by Hr incompatibility,² or A-B-O intragroup incompatibility,³⁻⁵ or by Rh subtype incompatibility where both mother and fetus are Rh positive but have different Rh phenotypes.^{1, 6, 7} In the same manner by which an Rh-negative mother may become immunized by the Rh-positive cells of the fetus and develop Rh antibodies, an Rh-positive mother may form antibodies against the fetal Rh-positive cells which are of a different phenotype than her own. For example, a mother with Rh' cells may have Rh₀ or Rh'' antibodies as the result of immunization by the Rh₀ or Rh'' cells of her fetus.

Since January, 1946, a special Rh clinic has been established at St. Catherine's Hospital. Every prenatal patient is tested for the Rh factor, and all Rh-negative mothers are referred to this clinic. Since the clinic has been fortunate in obtaining a supply of anti Rh', anti Rh'' and anti Hr' serums, as well as the standard anti Rh₀ serum, complete Rh typing is possible. Every Rh-negative mother with an Rh-positive husband is carefully studied and routine Rh-antibody determinations are made approximately every two weeks after the seventh month by both the agglutination and conglutination⁸ techniques. In addition, with the cooperation of the Department of Pediatrics, every newborn baby is carefully observed for jaundice or other signs characteristic of the syndrome of erythroblastosis fetalis. Babies in whom such signs appear are thoroughly investigated for blood incompatibility due to Rh, intra Rh, Hr, or A-B-O incompatibility.

In the course of these studies, erythroblastosis fetalis was diagnosed in two Rh-positive infants born of Rh-positive mothers in whom the etiological factor was intragroup Rh incompatibility. Since only a few such cases have been recorded in the literature, these cases are reported.

CASE 1.—P. L., white, 28 years of age, gravida i, para 0, with a normal prenatal course, was delivered Feb. 21, 1947, of a full-term living female, weighing 6 pounds 10½ ounces, by breech extraction, after a thirty-eight-hour labor. Nothing abnormal was noted at birth. The baby's condition was satisfactory until the evening of the fourth day when icterus and listlessness were first observed. Blood count the following morning showed red blood cells, 3,640,000; hemoglobin 14.9 Gm., with 1 per cent normoblasts present. Although both mother and infant were Rh positive, a diagnosis of erythroblastosis fetalis was

made and the baby was given a transfusion of 100 c.c. of Group A Rh-negative blood. A similar transfusion was given on the sixth day. The baby responded well and the jaundice cleared in a few days. On discharge, on the thirteenth day, the red blood cell count was 6,090,000, hemoglobin 20 Gm., with no normoblasts noted. Weight was 6 pounds, 5 ounces, and the baby has continued to do well since. Blood studies of the baby, mother, and father are in Table I.

TABLE I

| | BLOOD GROUP | ANTI Rh' SERUM | ANTI Rh'' SERUM | ANTI Rh ₀ SERUM | ANTI Hr' SERUM | PHENOTYPE |
|--------|-------------------|----------------|-----------------|----------------------------|----------------|---------------------------------|
| Baby | A ₂ MN | + | + | + | + | Rh ₁ Rh ₂ |
| Mother | O MN | + | - | + | + | Rh ₁ |
| Father | A ₂ N | + | + | + | + | Rh ₁ Rh ₂ |

The agglutination and blocking tests of the mother's serum for Rh antibodies were negative but the conglutination test was positive for Rh'' antibodies with a titer of 1 to 8. Group O Rh'' cells were used in all the antibody determinations. The maternal blood also had an anti A isoagglutinin titer of 1 to 2,048 and an anti B isoagglutinin titer of 1 to 8.

Comment: This is a case of erythroblastosis fetalis occurring in an infant born of an Rh-positive primigravida. Careful questioning of the mother elicited no history of previous transfusions or other blood therapy. Blood studies revealed a discrepancy between the Rh subtypes of the mother and infant. The mother lacked the Rh'' radical which the infant inherited from her father. Rh'' antibodies with a titer of 1 to 8 were demonstrated in the mother's serum by the conglutination technique. Although there were also present the requisites for A-B-O isoimmunization—mother group O, baby group A, with the mother's serum having an anti A isoagglutinin titer of 1 to 2,048—it is believed that the predominant etiological factor was the subtype Rh'' isoimmunization.

CASE 2.—B. W., white, 28 years of age, gravida ii, para i, delivered a seven months premature female spontaneously, Feb. 5, 1947. Delivery was complicated by a marginal placenta previa which was treated by simple rupture of the membranes and a transfusion of 750 c.c. of Rh-negative blood. The patient was originally considered Rh negative on the basis of a test by the standard anti Rh₀ serum. The infant was in good condition at birth, but was placed in an incubator on the usual premature regime. Her condition was satisfactory until the third day, when jaundice was observed. Blood count was red blood cells, 5,720,000; hemoglobin, 22 Gm. with 10 per cent normoblasts. A diagnosis of erythroblastosis fetalis was made and, since repeated blood counts showed no significant drop in red blood cells or hemoglobin, no transfusions were given. The jaundice persisted for eight days, gradually fading. The infant continued to thrive and gain weight. However, further blood counts showed: On March 22, six weeks after birth, red blood cells were 3,890,000, hemoglobin, 13.9 Gm.; on March 24, red blood cells were 3,730,000, hemoglobin, 12 Gm.; on March 31, red blood cells were 2,730,000, hemoglobin 9.9 Gm.; and on April 1, red blood cells were 2,530,000, hemoglobin, 9.2 Gm. At the age of eight weeks Rh-antibody study of the infant's serum disclosed the presence of Rh₀ antibodies with a titer of 1 to 128 by the agglutination technique and a titer of 1 to 16 by the conglutination technique. A transfusion of 80 c.c. of Rh-negative Group O blood was then given, and a similar transfusion of 85 c.c. two days later. During this time no clinical jaundice was noted, although the infant's icterus index was 25. The baby responded well to transfusion and continued to gain weight. Examination of the blood on April 7 revealed no antibodies. The baby was

discharged in excellent condition on April 12, weighing 5 pounds, 8 ounces, with red blood cells 5,900,000, hemoglobin 23.4 Gm., and has continued to do well.

Blood studies of the baby, mother, father, and brother are as follows:

TABLE II

| | BLOOD GROUP | ANTI Rh' SERUM | ANTI Rh'' SERUM | ANTI Rh ₀ SERUM | ANTI Hr' SERUM | PHENOTYPE |
|-------------|-------------|----------------|-----------------|----------------------------|----------------|---------------------------------|
| Baby | O | + | + | + | + | Rh ₁ Rh ₂ |
| Mother | A | + | + | - | + | Rh' Rh'' |
| Father | O | + | + | + | + | Rh ₁ Rh ₂ |
| First child | A | + | + | - | + | Rh' Rh'' |

The agglutination and blocking tests of the mother's serum for Rh antibodies were negative but the conglutination test was positive for Rh₀ antibodies with a titer of 1:256. Group O Rh₀ cells were used in all the antibody determinations.

Comment: This case presents a classical picture of intra Rh incompatibility. The mother, although Rh positive, lacked the Rh₀ radical found in the baby's red cells. Her serum had anti Rh₀ antibodies with a titer of 1 to 256. Since the firstborn child had the same Rh phenotype as the mother, isoimmunization to the Rh₀ radical could not have occurred as the result of the first pregnancy. There was no history of previous transfusion to the mother. Consequently, the mechanism of isoimmunization in this case is similar to that occurring in a primigravida. An important finding in this case was the discovery of the Rh₀ antibodies in the baby eight weeks after birth. These antibodies were responsible for the progressive anemia. So far as we have been able to ascertain, this persistence of antibodies in the infant for so long a period of time has not been reported previously.⁹

Discussion

These two cases show that erythroblastosis fetalis does occur in infants born of Rh-positive mothers. Case 1 demonstrates that this syndrome may be present in the firstborn child. Obstetricians should be aware of this possibility, and family blood studies should be done in all cases of jaundice occurring in newborns. While it would be impractical to study prenataally Rh-positive mothers for antibody formation, nevertheless their babies should be observed for signs of erythroblastosis fetalis. In addition, Rh-negative primiparas with Rh-positive husbands should be examined for antibodies as carefully as Rh-negative multiparas. Complete reliance cannot be placed on a history of no previous blood therapy in primiparas, as it is entirely possible that blood may have been given to them early in infancy, unknown to themselves or their parents.

In Case 2, on the basis of testing with the standard 85 per cent anti Rh₀ serum, the mother would ordinarily be classified as Rh negative and the infant's erythroblastosis ascribed to the usual Rh incompatibility. Undoubtedly, study of such cases in the past with anti Rh' and anti Rh'' serums would have disclosed other instances of intra Rh incompatibility. Since both of these serums are now available, more complete studies of the etiology of erythroblastosis fetalis can be made in the future.

The question of what kind of blood should be used in the therapy of these erythroblastotic infants and their mothers is of great importance. Blood of the

same Rh phenotype as the mother's would be ideal. Such blood, however, may be difficult to obtain. Since the serums of both infant and mother, although classified as Rh positive, contain Rh antibodies, it is more practical and easier to transfuse with Rh-negative blood than to obtain Rh-positive blood of the exact phenotype as the mother's. Thus, therapy for the infant should consist of Rh-negative blood, and, if transfusion is necessary for the mother, similar blood should be used. However, it is imperative that the Rh-negative blood used for transfusion in these cases should be classified as such on the basis of testing with the three Rh antisera (anti Rh₀, anti Rh' and anti Rh'') and not on the usual basis of testing with the standard anti Rh₀ serum. Serious complications may occur if this precaution is not observed. To illustrate, in Case 1, both mother's and infant's serum contained Rh'' antibodies. If blood classified as Rh negative after testing with the usual anti Rh₀ serum, but nevertheless containing Rh'' cells, had been given to the mother, a severe hemolytic transfusion reaction would have occurred. If the same blood had been given the infant, the erythroblastosis would have become more severe.

We believe it important to note that the same precaution should be observed in the designation of Rh-negative blood when transfusing cases of erythroblastosis due to true Rh incompatibility. The antibodies present in the serums of both mother and child may be Rh₀, Rh' or Rh'' in type. The use of so-called Rh negative blood containing Rh' or Rh'' cells might have serious consequences.

It is interesting to speculate on the reason for the persistence of antibodies for eight weeks after birth in the infant in Case 2. Perhaps the red cells of a premature infant absorb or react more slowly to antibodies. Perhaps the X protein postulated by Wiener⁹ as necessary for the reaction of certain types of antibodies with red cells is insufficient or only weakly active in prematures. Certainly more study remains to be done on the period of time of persistence of antibodies in the newborn and the reason thereof.

The clinical course of these two cases which responded well to blood transfusions confirms the accepted opinion that erythroblastosis fetalis due to intra Rh incompatibility is less severe than when caused by true Rh incompatibility. This is due apparently to weaker antibodies. Two cases of erythroblastosis due to A-B-O incompatibility now being studied are also of a less serious nature. These observations will be reported subsequently.

Conclusions

1. Erythroblastosis fetalis does occur in infants born of Rh positive mothers, and also in infants born of primigravida.

2. Blood for transfusion of both mother and child, where erythroblastosis has occurred, must be classified as Rh negative on the basis of negative testing with anti Rh₀, anti Rh' and anti Rh'' serums.

3. Rh antibodies have been found to persist in a titer of 1-256 in an erythroblastotic infant for as long as eight weeks after birth.

4. All newborn babies with jaundice should be investigated for blood incompatibilities.

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Addendum

Since this paper was submitted for publication, we have observed two additional cases of erythroblastosis in infants born of Rh-positive mothers. In one case, Rh₀ antibodies were found; in the other, Rh" antibodies.

ERYTHROBLASTOSIS FETALIS IN THE INFANT OF A PRIMIGRAVIDA

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ALTHOUGH erythroblastosis fetal^{is} in the firstborn is by no means unknown,¹ it is rare to find the condition, especially in the hydropic form, in the firstborn where there is no history of previous pregnancy or blood injection. Such a case is herein reported.

Levine and Waller¹ collected and reported nineteen mothers who had delivered their firstborn with erythroblastosis fetal^{is}. These mothers had previously been transfused with blood without regard to the Rh factor. There is also presented, in the same paper, a group of nine cases of erythroblastosis fetal^{is} in the firstborn of mothers not previously transfused. These infants were presumably Rh positive. In only one of these latter cases, however, was the blood of the mother positive for anti-Rh agglutinins, and the firstborn of this mother is listed as having erythroblastosis fetal^{is} mild enough to need no treatment.

The case which I am reporting differs from those listed by Levine and Waller¹ in that: (1) There had been no previous pregnancies; the cervix was distinctly nulliparous. (2) Diligent questioning of the patient and the patient's family revealed not the slightest hint of blood by vein, or by injection subcutaneously, intramuscularly or intraperitoneally. (3) This patient showed anti-Rh_o agglutinins in a dilution of 1:64, and (4) delivered a macerated, hydropic fetus.

Mrs. F. F. O. first came to the author's attention April 17, 1945, because of amenorrhea, frequency of urination, and enlargement of her breasts; her last menses began Dec. 3, 1944, and fetal movements had been felt one week prior to her initial visit. Her past, family, menstrual history, etc., were notable only for the absence of relevant positive data; she was one of five children all of whom were healthy. The patient's husband was in good health, 38 years old, weighed 165 to 170 pounds, and was 5 feet 11 inches tall.

Physical examination revealed that this 38-year-old primipara was 5 feet 2½ inches tall, weighed 143 pounds, had a blood pressure of 115/60, and a systolic mitral murmur. Her pelvic measurements were within normal limits, and nothing was found on bimanual examination except an intrauterine pregnancy of 18 weeks' duration. Laboratory work was negative save for a lowering of the hemoglobin to 13.5 Gm. (17 Gm. = 100%).

Because of the heart findings, a cardiologist was asked to see the patient. He reported a normal x-ray study of the chest, normal electrocardiogram, and added "we would be justified in not imposing any special restriction on account of the heart."

With the above in mind, the patient was treated as a normal expectant mother. Milk, vitamin D, and ferrous sulfate were prescribed, later to be replaced by medication containing dicalcium phosphate, viosterol, and ferrous sulfate. Urine, weight, and blood pressure remained normal as the pregnancy advanced, but in spite of iron therapy, a check on the patient's hemoglobin, June 19, 1945, showed the same level as the initial reading of 13.5 grams. When seen July 10, 1945, her blood pressure was 115/60, weight 152½ pounds, showing a gain in three months of 9½ pounds. In the next two weeks, however, the patient gained 5 pounds, and was placed on a dietary regime markedly restricting the calories.

On Aug. 1, 1945, five weeks before the expected date of confinement, a spontaneous rupture of the membranes occurred. This was followed in four hours by the onset of labor and admission to St. Luke's Hospital.

On admission, contractions of the uterus were occurring every two to three minutes and lasting thirty seconds. The fundus uteri (McDonald) measured 34 cm. Heart, lungs, blood pressure, temperature, pulse, and respiration were normal, but no fetal heart sounds were heard. One hour after admission to the hospital, rectal examination revealed the cervix 5 cm. dilated, with the vertex just below the ischial spines. Twenty minutes later the head was almost on the perineum with no cervix palpable. Forty-five minutes of second stage labor yielded no progress, and examination revealed the head to lie in a L.O.T. position with antepartum fetal death. This had been suspected by the absence of fetal heart sounds, and was confirmed by finding maceration of the scalp. The head was manually rotated with ease to an anterior occiput, and an easy low forceps served to complete delivery of the head. Moderate difficulty was experienced in the extraction of the shoulders and abdomen. The diagnosis of fetal hydrops seemed obvious. Weight of the baby was 9 pounds 2 ounces.

At the time this patient was under observation, it was the author's practice to secure Rh determinations only on multiparas who had had previous stillbirths or neonatal deaths. Blood was drawn immediately after the delivery and reported Rh negative, blood group A, and the husband blood group B, Rh positive. Dr. Levine further reported the blood of the patient as follows: "The blood shows strong anti-Rh₀ agglutinins in a dilution of 1:64; Group A, Rh⁺, Hr. positive." The patient later donated 500 c.c. of blood, the anti-Rh₀ serum from which was used successfully for Rh typing.

Intrapartum and postpartum blood loss was minimal, and it was not necessary to transfuse the patient. On the sixth postpartum day the hemoglobin was 70 per cent Sahli, with 3,710,000 red blood count. Ferrous sulfate was depended upon to correct this slight anemia. There were no complications, and the patient was discharged in good condition. At the six-week check-up the hemoglobin had risen to 90 per cent Sahli.

Essential findings in the pathologic examination of the baby and placenta were as follows:

The baby was a term female with markedly distended abdomen over which the skin was thick, edematous, and macerated. The peritoneal, pleural, and pericardial cavities were filled with bloody fluid. The liver and spleen were considerably enlarged, but microscopic examination was not informative because of marked autolysis. However, near the capsule of the liver, numerous normoblasts were to be seen. The other organs were essentially normal.

The placenta measured 28 by 19 by 4 cm., and was firm, yellowish-white, and meaty. Microscopically, the cuboidal cells lining the villi were young in appearance, and the villi contained large pale young cells characteristic of the placenta of erythroblastosis. Anatomical diagnosis was erythroblastosis fetalis with hydrops.

Summary and Conclusions

1. Severe erythroblastosis fetalis (fetal hydrops) can occur in primigravidas who have not previously received blood in any manner.

2. Rh determinations should be made on all pregnant women, and Rh antibody studies made on all pregnant Rh-negative women in the latter weeks of gestation.

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820 WEST FRANKLIN STREET

TRAVEL IN PREGNANCY

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OBSTETRICIANS are not in complete agreement as to how much the pregnant woman may travel without danger to the pregnancy. The practice of our departmental staff is to permit travel by plane, Pullman, or ocean steamer up to the thirty-fourth week. However, before any long trip is made the patient is examined vaginally to determine the condition of the cervix. Travel by automobile is permitted up to a maximum of 300 miles per day with an adequate rest period of at least two hours at the end of 150 miles. With these restrictions, long automobile trips are permitted. If the patient has shown any evidence of a threatened abortion or has a history of abortion or premature labors, travel by any means is restricted or forbidden. During the war there was so much travel by pregnant women that it became obvious that the instructions were too restricting. It was, therefore, deemed advisable to gather further information on this subject of travel in pregnancy.

Diddle, in September, 1944, published a paper on this subject. His data were collected on obstetric dependents of armed forces personnel. He was located on an island 127 miles from the mainland and connected by a rough asphalt and coral highway. The nearest railway was 170 miles away on the mainland. In order to commute from the island to the mainland the patients had to travel over this highway by car or bus. In his series, of 289 women who traveled before the fourth month, 16, or 5.6 per cent, aborted or threatened to abort; whereas 17.9 per cent of the nontravelers aborted or threatened to abort. Only one patient of his seemed to abort from travel in itself. This was the case of a woman who had taken a motorcycle ride a few hours previously. His conclusions were that neither the distances covered, nor the method of travel, nor the time of month a journey was undertaken revealed any significant differences in the incidence of abortion.

In the Chicago Lying-in Hospital over a period of approximately two and one-half months, 681 patients were interviewed a few days following delivery. They were asked for the following information: (1) whether they had traveled at any time during their pregnancy, (2) where they traveled, (3) date of their trip, (4) method of travel, and (5) discomfort or illness during or immediately following the trip.

This group of 681 patients can be divided into the following groups:

| | |
|--------------------------------------|-----|
| 1. no travel in present pregnancy | 337 |
| 2. traveled in present pregnancy | 309 |
| 3. abortion with no travel preceding | 18 |
| 4. abortion with travel preceding | 17 |
| total | 681 |

These patients were also asked regarding previous pregnancies in which they had traveled and in a few instances concerning previous abortions. These additional pregnancies bring the total to 719 pregnancies studied.

These 719 pregnancies can be divided into the following groups:

| | |
|--------------------------------------|------------|
| 1. no travel | 337 |
| 2. traveled during pregnancy | 341. |
| 3. abortion with no travel preceding | 24 |
| 4. abortion with travel preceding | 17 |
| total | <u>719</u> |

An abortion is considered in this survey as any termination of pregnancies prior to twenty-eight weeks. As to the criteria as to whether a patient traveled, a patient is placed in the no travel category in this survey unless the trip was 100 miles or farther. There are a few exceptions to this in the case of some patients who made numerous trips of short distances. They will be discussed individually later in this report. In the case of abortions any trip other than ordinary short rides around the city places the patient in the traveled category regardless of whether the trip was 100 miles or not.

It is acknowledged that there are many limitations in this survey, limitations which are unavoidable because of their complexity. Among these limitations which influence the accuracy of this report are the type of roads over which the patient traveled, and if the trips were made by going for long hours at a time without rest stops, and many other factors which are difficult to record statistically. The first portion of this survey will be devoted to the non-abortive cases, and the second portion to the abortions.

Table I gives the percentage of total number of pregnancies with traveling in each lunar month by various methods. The peak of traveling was reached in the seventh month. The greatest part of the traveling was done by automobile and train, with very little by bus.

As to the distances traveled by these women there was no large concentration of a group of women having traveled a short distance or a long distance. There is one exception to this in the distances traveled by automobile in the 100 to 199 mile category for all months and in the 100 to 299 mile category for the sixth through the ninth months. In this instance there is a large group of women having traveled less than 300 miles. Other than this the distances traveled by these women are spread rather evenly from 100 miles to over 3,000 miles.

As to plane travel, most of the distances traveled are large as is to be expected, due to the inability to take short plane trips on most airlines.

Bus travel was used mainly for short trips, very few patients taking long trips by this method.

Of the boat trips, there were only three—one each in the fourth, fifth, and sixth lunar months. The trip in the fourth lunar month was an ocean voyage from England to New York. The other two boat trips were Great Lakes vacation cruises.

Several of the patients traveled a good deal throughout their pregnancies with no apparent ill effects.

Patient K. M., No. 390168, traveled by train from New York to Boston in the sixth month; from Boston to Los Angeles in the seventh month; from Los Angeles to San Francisco in the ninth month; and from San Francisco to Chicago in the tenth month.

Patient A. T., No. 381713, lives in Champaign, Ill. She traveled by train to Chicago and return (276 miles round trip) every three weeks for her clinic visits from the fifth month to the time of delivery.

Patient L. C., No. 378751, traveled by car 150 miles every weekend during her pregnancy.

Patient A. K., No. 375491, traveled by car between Chicago and St. Louis, Mo. (600 miles round trip) every three weeks during her second, third, fourth, fifth, sixth, and seventh months.

TABLE I

| MONTHS GESTATION | PERCENTAGE OF TOTAL PREGNANCIES WITH TRAVELING | TYPE OF TRAVEL |
|------------------|--|----------------|
| 1 | 3% | car |
| | 1.6% | train |
| 2 | 3.6% | car |
| | 2.2% | train |
| | 0.2% | plane |
| | 0.1% | bus |
| 3 | 3.6% | car |
| | 3.6% | train |
| | 0.8% | plane |
| | 0.1% | bus |
| 4 | 5.5% | car |
| | 4.8% | train |
| | 0.8% | plane |
| | 0.2% | bus |
| | 0.1% | boat |
| 5 | 5.0% | car |
| | 5.0% | train |
| | 1.3% | plane |
| | 0.1% | bus |
| | 0.1% | boat |
| 6 | 7.0% | car |
| | 5.0% | train |
| | 1.2% | plane |
| | 1.1% | bus |
| | 0.1% | boat |
| 7 | 9.3% | car |
| | 6.1% | train |
| | 0.9% | plane |
| | 0.7% | bus |
| 8 | 9.1% | car |
| | 4.5% | train |
| | 0.7% | plane |
| | 0.7% | bus |
| 9 | 6.9% | car |
| | 2.5% | train |
| | 0.4% | plane |
| | 0.1% | bus |
| 10 | 2.0% | car |
| | 1.2% | train |
| | 0.1% | plane |

Patient M. H., No. 388642, in her first pregnancy traveled by train from Washington, D. C. to Chicago (700 miles) in the first month; from Chicago to Miami (1,391 miles) by train in the third month; from Miami to Washington, D. C. (1,117 miles) by train in the third month; from Washington, D. C. to Norfolk, Va. (175 miles) by automobile in the fourth month; from Norfolk, Va., to Washington, D. C. to Chicago (875 miles) in the fifth month by train; and from Chicago to Miami (1,391 miles) by train in her eighth month.

Patient C. B., No. 380263, made five plane trips between Chicago and Kansas City (1,500 miles round trip) during the third, fourth, and fifth months.

There are many other patients who traveled extensively during their pregnancy, and those listed above are but a few examples.

Attention can now be given to the various methods of travel. In general, patients found that, when traveling by car, short hours of driving with frequent rest stops left them feeling much less fatigued than when driving continuously for several hours.

In traveling by train, streamliners and Pullman accommodations were much preferred; the patients traveling by coach becoming fatigued, nauseated etc., much more readily. Those that traveled by bus did not find it as comfortable as traveling by Pullman or private car.

The technique of Hesseltine and Hopkins² was employed. The test strain was an 18- to 24-hour 5 per cent glucose broth culture. The concentration of the respective chemicals and the vehicle for the compounds are indicated in the table. Equal amounts of the suspended broth culture were placed in the test tubes containing the medicament. Each tube was agitated immediately after the addition of the agent to insure thorough mixing. After five minutes' exposure a loop (size 3) of material was transferred to a petri dish. Sabouraud's agar media was poured immediately and the plates rotated to complete the seeding. Observations were made for several days and compared to control plates. Actually the forty-eight hours' reading were thoroughly reliable. Four plus equaled the control, with graduations down through 3, 2, and 1 plus for decrease growth of organism while 0 means no growth. Final concentrations were one-half of the original.

TABLE I. THE FUNGICIDAL POTENCY OF COMPOUNDS UPON MONILIA CULTURES (6225) IN GLUCOSE BROTH AND IN GLUCOSE BROTH TO WHICH HUMAN SERUM AND CELLS HAVE BEEN ADDED.

| | CONCENTRATION PER CENT | VEHICLE | BROTH GROWTH | VEHICLE | CELLS AND SERUM GROWTH |
|---|------------------------|--------------------|--------------|------------------|------------------------|
| 1. Ricinoleic acid | 0.75 | alc. 95% | - | alc. 95% | - |
| | 2.0 | gly. 90%, alc. 10% | + | gly. | - |
| 2. Propyl para hydroxybenzoate | 0.1 | alc. 50% | - | | + |
| | 1.0 | gly. 90%, alc. 10% | - | gly. | |
| 3. Oxyquinoline sulfate | 0.025 | H ₂ O | ++ | | |
| 4. Stearic acid | 5.0 | alc. 95% | - | alc. 95% | + |
| 5. Cetyl alcohol | 0.5 | alc. 95% | - | gly. | ++++ |
| 6. Cetyl dimethyl ammonium chloride | 0.2 | H ₂ O | + | H ₂ O | - |
| 7. Cetyl diethyl ammonium chloride | 2.0 | H ₂ O | - | H ₂ O | - |
| 8. Cetyl (di-N-Butyl) ammonium chloride | 0.2 | H ₂ O | + | H ₂ O | - |
| 9. Triethanol amine | 0.25 | H ₂ O | ++++ | | |
| 10. Sulfamic acid | 0.1 | H ₂ O | +++ | | |
| 11. Calcium propionate | 10.0 | H ₂ O | ++++ | | |
| 12. Sodium propionate | 10.0 | H ₂ O | ++++ | | |

Alc. = alcohol; Gly. = glycerine; H₂O = water. Final concentration of material is one-half.

Those that held promise were subjected to more rigid test by adding blood cells and serum. It has been demonstrated that 50 per cent to 95 per cent ethyl alcohol has some fungicidal action. It should be pointed out also that ethyl alcohol in these concentrations causes irritation of the vaginal mucous membranes and is unsuitable for this organ. These two factors were eliminated by using glycerine as the sole or major substitute for the alcohol soluble compounds. A mixture of 90 per cent glycerine and 10 per cent ethyl alcohol served as a satisfactory vehicle in instances where glycerine alone was not satisfactory.

It has not been demonstrated that complete killing in five minutes is necessarily the best approach for in vivo application but prompt lethal action has received the most attention. Nevertheless previous tests have had partial confirmation by clinical responses to the in vitro lethal materials.

LOW MATERNAL MORTALITY WITH PERSISTENCE OF HEMORRHAGE AS THE CHIEF CAUSE OF DEATH; AN ANALYSIS OF PUERPERAL DEATHS IN BROOKLYN DURING 1946*

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THE importance of a program for the prevention of mortality in childbirth can be best shown by comparison of the maternal death rate of Brooklyn for 1946 with the rate for 1937, the year the Brooklyn Committee on Maternal Welfare began its analysis of maternal deaths.

In 1937 there were 164 puerperal deaths in Brooklyn, and the maternal death rate was 40.7 per 10,000 live births. In 1946 this rate had fallen to 8.7, and there were but 57 puerperal deaths. It would appear that if the maternal death rate of 1937 had not been reduced, 187 more women in Brooklyn would have died of childbirth in 1946 alone.

A reduction of 80 per cent is notable, even though maternal death rates are declining generally. The latest figure available for the United States (1944) is 23 per 10,000 live births. The puerperal mortality rate for the entire City of New York in 1946 was 10.4 per 10,000 reported terminated pregnancies. This figure for 165,716 total births in this city of nearly eight million people is extraordinarily good. The rate for Brooklyn has been the lowest of the five counties included in New York City for the past three years (Fig. 1).

Our Brooklyn experience is of more than local importance. Our critical analyses of the causes of maternal mortality do not depend solely upon the factual data of certificates of death. The case records in our files vary in quality, and data essential to a good case report are often lacking, yet the controllable factors of death are usually found. It may be said with confidence that deductions made from statistical tabulations based upon the meager information on the certificate of death can never be more than generalized.

More births occur in Brooklyn than in more than half of the individual states. More babies are born in Brooklyn than in any other borough of the City of New York, more than in Philadelphia, and nearly three times as many as in Boston. There are few states comparable to the City of New York, and but few cities of the United States comparable to Brooklyn alone. (Table I.)

In 1946, fifty-seven deaths in Brooklyn were assigned to puerperal causes by the Bureau of Records and Statistics of the Department of Health of the City of New York. The causes of death are listed in Table II, and comparison is made with the two previous years.

Nonwhite Deaths^a

The nonwhite population of New York City is an important statistical factor, since the puerperal death rate of Negro women in 1946 was two and one-half times that of white women, while their death rate from abortion was more than ten times as great. In Brooklyn the puerperal mortality rate for Negro women was nearly twice as high as the white, and their abortion mortality

*Read at a meeting of the Brooklyn Gynecological Society, May 2, 1947.

Those patients traveling by plane preferred that method, especially those who had also traveled by other methods during their pregnancy. There were a few cases of nausea and vomiting, but these occurred when the plane trip was made in bad weather.

Abortions

As regards the abortions, 24 occurred in women giving no history of having traveled at any time during their pregnancies. In addition, ten of the patients who went to term had spotting during their early months but had done no traveling up to the time of the spotting. This makes a total of 34 abortions and threatened abortions who give no history of travel.

Seventeen patients gave a history of having traveled at some time prior to their abortion. In addition, two patients who went to term had spotted in early pregnancy immediately following a trip—one after a 600 mile train trip in her fifth month; the other following a short automobile ride over a very rough road in her third month. This gives a total of 19 abortions and threatened abortions in whom a history of traveling is given.

In condensed form:

| | | |
|--------------------------------------|----|--------|
| 1. patients with no travel | 34 | 64.2% |
| 2. patients with a history of travel | 19 | 35.8% |
| total | 53 | 100.0% |

Of the 19 cases of abortions and threatened abortions in women who traveled, only eight had traveled at any time near enough to the onset of symptoms for the traveling to have been a possible factor. In four of these cases the onset of symptoms immediately followed the trip, and of these four patients, two went on to a full-term pregnancy.

Therefore, there are two cases which actually aborted and in whom the onset of symptoms was immediately preceded by a trip. Whether or not these patients, or the others for that matter, would have aborted if they had not traveled is impossible to say. In four cases, however, it seems definite that the trip was the immediate precipitating factor of symptoms even though other factors may have been involved.

Conclusions

In 339 pregnancies traveling was done without any threat of abortion. In two additional cases threatened abortions were probably the result of a trip, but the pregnancies went on to term.

In 17 abortions with a history of traveling, only six had traveled near enough to the time of onset of symptoms to be a possible factor.

Hence, of all 358 patients who traveled, in eight or 2.2 per cent, could the trip have been a factor in threatening or producing abortion, and in four, or 1.1 per cent could the trip be said to be the immediate precipitating factor. Of this latter group of four, two, or 0.6 per cent, actually aborted, the other two going on to term.

From the extent of traveling done by pregnant women in all stages of their pregnancies without complications, it would appear that traveling is not harmful to the majority.

Reference

1. Diddle, A. W.: AM. J. ORST. & GYN. 48: 354-360, 1944.

TABLE I. STATISTICAL IMPORTANCE, NEW YORK CITY AND BROOKLYN, 1944
LIVE BIRTHS (IN THOUSANDS) BY PLACE OF OCCURRENCE

| NEW YORK CITY | 122 | BROOKLYN | 44 |
|---------------|-----|--------------|----|
| STATES | | CITIES | |
| New York | 229 | Los Angeles | 66 |
| Pennsylvania | 178 | Chicago | 59 |
| California | 177 | Philadelphia | 38 |
| Texas | 164 | Detroit | 35 |
| Illinois | 139 | Boston | 18 |
| Ohio | 132 | | |

TABLE II. MATERNAL DEATHS (BROOKLYN, 1946)

| CAUSE | | 1946 | 1945 | 1944 |
|--------------------|---------|--------|--------|--------|
| Abortion | 140-141 | 7 | 11 | 10 |
| Ectopic | 142 | 2 | 2 | 3 |
| Hemorrhage | 134-146 | 8 | 13 | 8 |
| Toxemia | 144-148 | 12 | 5 | 11 |
| Infection | 147 | 12 | 17 | 20 |
| Accidents of labor | 149 | 11 | 10 | 8 |
| Other | 145-150 | 5 | 9 | 2 |
| Total | | 57 | 67 | 62 |
| Total births | | 64,559 | 54,293 | 51,082 |
| Rate | | 8.7 | 12 | 12.2 |

rate eight and one-half times as high as that of white women. The puerperal mortality rates for all boroughs are corrected for color according to the 1940 census population. All New York puerperal mortality rates are calculated from the number of reported terminated pregnancies. This is done nowhere else in the United States. Whether this statistical method is better than the usual live birth ratio, is, in my opinion, doubtful (Fig. 2).

Nonpuerperal Deaths¹⁵

It is common practice, in analysis of deaths associated with childbirth, to pay no attention whatever to those not assigned by the statistician directly to puerperal causes, since no matter what they include or how many there are they do not affect the maternal death rate. No good program can be planned, however, without study of these deaths, if only because a large number of deaths due to cardiac disease will not otherwise be found. The total number of deaths associated with childbirth, but officially assigned to nonpuerperal causes, in 1946 was fifteen. Two suicides are included, one after cesarean section, the other during labor. In nine cases death was due to Rheumatic heart disease.

Deaths Early in Pregnancy

Death was due to ectopic pregnancy in two cases, and seven cases were assigned to abortion.

In the ectopic cases, death was due to failure of diagnosis in both cases. In one case in which diagnosis had been missed by two physicians, the third found the patient dead in bed at home. In the other case death followed laparotomy, after curettage in another hospital.

In four cases abortion had been induced, with perforation of the uterus and intestinal injury in two cases; in two others in which hemorrhage was profuse for several hours, death was finally due to infection. Included is a case of eclampsia in the twenty-seventh week, in which labor was induced by manual dilatation and bougie after several convulsions and fetal death.

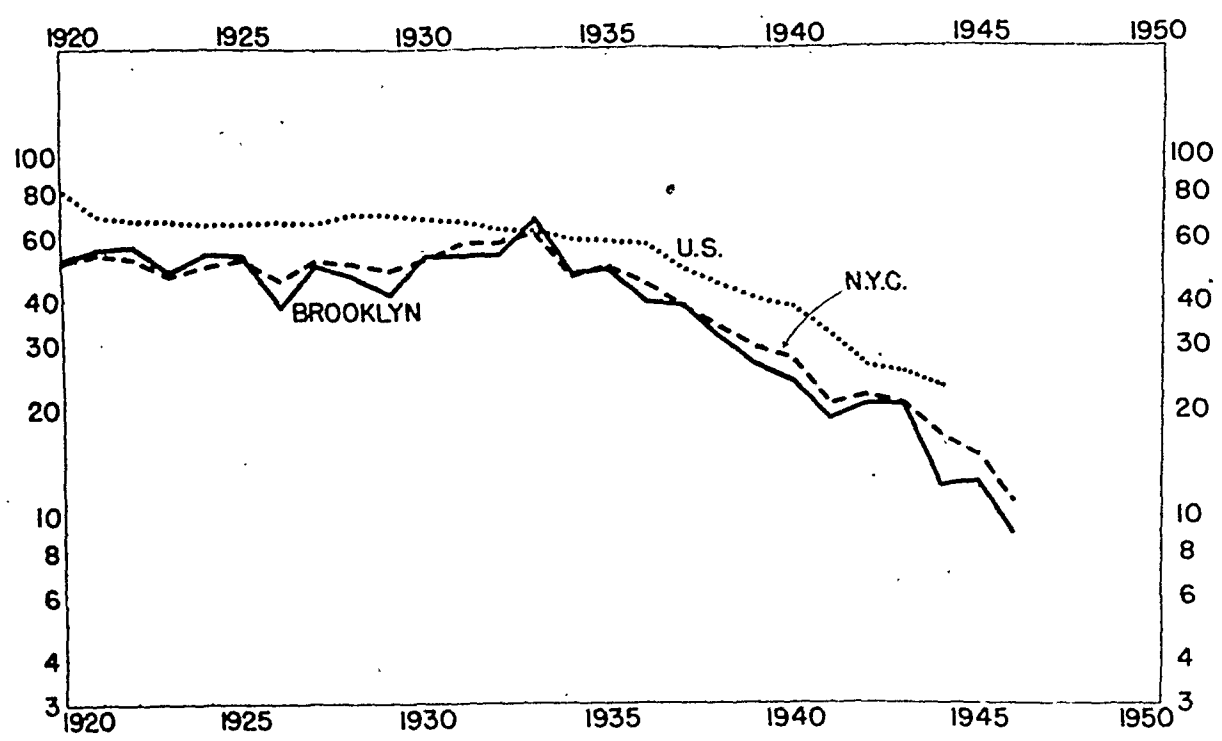


Chart 1.—Puerperal mortality of United States, rate per 10,000 live births; city of New York, rates per 10,000 total births; and Brooklyn, rates per 10,000 total births.

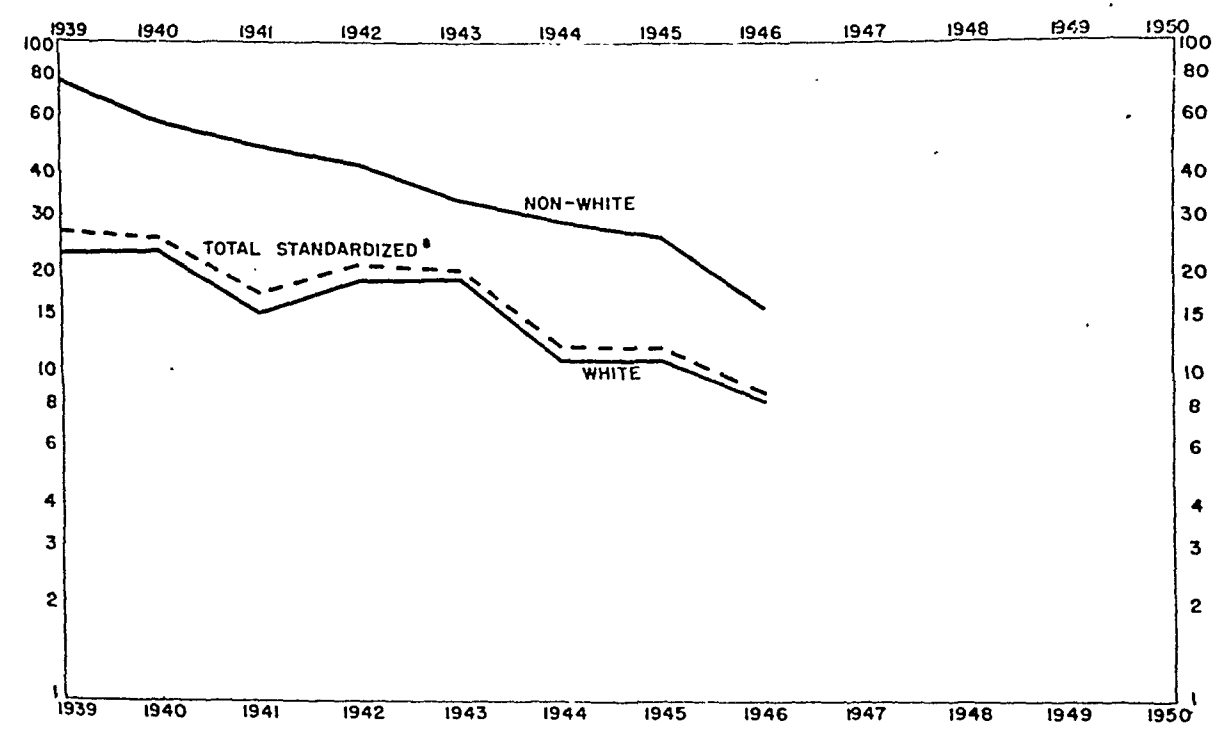


Chart 2.—Borough of Brooklyn puerperal mortality, rates per 10,000 total births—according to color.

*Corrected for color—Distribution of New York City population according to color, 1940 census.

Cesarean Section

Cesarean section was associated with death in seventeen of the total number of seventy-two deaths, or in fourteen of the fifty-seven deaths assigned to puerperal causes. It is curious that death was due to infection in but three cases. In three cases in the nonpuerperal group death was due to Addison's disease, suicide, and cardiac disease; and in the puerperal group to eclampsia (one), uremia (one), aspiration asphyxia (one), atelectasis (two), cardiac disease (two), transfusion (two), spinal anesthesia (one), and infection (three). All three deaths from infection followed the lower segment operation, two after long labor; in the other case death on the eleventh day followed operation upon a patient whose hemoglobin was 40 per cent; 500 c.c. of plasma were administered just prior to operation, and 500 c.c. of blood immediately afterward; at autopsy thrombosis of the left common iliac vein and pulmonary embolism were found.

Anesthesia

It is not possible to learn the true importance of anesthesia from statistics of maternal death. Even though death is stated to have been directly due to aspiration of vomitus, anesthesia is not tabulated as a cause of death. Only from case records can the frequency of death from anesthesia be discovered. Its importance is not widely appreciated.

Anesthesia was an important cause of death in Brooklyn in 1946. Deaths may be readily separated into three groups as due to the toxic action of the anesthetic drug, to aspiration asphyxia, and to atelectasis, whether from aspiration or not. These deaths are of so great importance that the essential data of each case are reported.

CASE 1.—Age 18 years, cardiac, in labor four hours at term. Classical cesarean section under spinal anesthesia. Sudden death occurred with delivery of the child, twelve minutes after administration of 50 mg. of procaine.

Four deaths were due to aspiration asphyxia.

CASE 2.—Age 27 years. Extraperitoneal cesarean section under gas, oxygen, ether sequence after fifty hours of labor. At completion of the operation, vomiting occurred. Labored breathing and deep cyanosis followed. Death occurred during laryngeal suction.

CASE 3.—Age 41 years. Under gas, oxygen, ether anesthesia hysterectomy for rupture of the uterus had been nearly completed when vomiting occurred. Anesthesia was forced at this point and sudden death followed, despite removal of a large amount of material from the trachea and bronchi through a bronchoscope.

CASE 4.—Age 27 years. Low forceps delivery under gas, oxygen, ether sequence after seven hours of labor. Vomiting occurred during repair of episiotomy. Dyspnea and cyanosis followed. Death occurred twenty-four hours later with a temperature of 103° F., pulse 145, and respiration 48. X-ray showed "massive bilateral pneumonia."

CASE 5.—Age 32 years. Breech extraction under open ether anesthesia. As soon as anesthesia was discontinued cyanosis deepened rapidly, bloody froth appeared at the mouth, and death occurred in twenty minutes.

Atelectasis follows bronchial obstruction or decreased ventilation of the lung field. Mucus is aspirated more often than vomitus, yet aspiration is not essential. There were three cases in which the atelectasis syndrome appears to be typical. Essential data follow:

Toxemia

Officially assigned to toxemia were twelve cases; three more were found in the infection group, and one in the abortion group. Prenatal care was inadequate in all but two cases. One patient with eclampsia was but 15 years of age. In three cases hemorrhage was said to have been considerable, though death was due to eclampsia. Convulsions occurred in nine cases. Cesarean section was performed five times, in two cases after convulsions.

Infection

Included in this group of twelve cases are three deaths due to cardiac disease, since death had been attributed to pulmonary embolism. Altogether, embolism was mentioned in ten of the twelve cases assigned to infection. A case of eclampsia is included, and three cases of death shortly after delivery in which dyspnea, paroxysmal cough, and cyanosis point to anesthesia as the cause.

The statistical rule which, since 1940, has assigned embolism to infection as a cause of death unduly weights this figure. Sudden death shortly after delivery is more often due to a cause other than embolism. Statistics may show that there has been no statistically significant decrease in the puerperal septicemia rate of the City of New York, and that improvement has been effected to a large extent by a decrease in deaths from all causes other than infection. Our opinion is otherwise.

In but one case of embolism was this diagnosis proved by autopsy. In one case in which death occurred under anesthesia within half an hour of delivery, cerebral embolism was said to be the cause. In two cases, clinical embolism occurred on the third and fifth days in women who were up and about.

Hemorrhage

Formally assigned to hemorrhage were but eight deaths. In two of the three cases of postpartum hemorrhage, hysterectomy was performed after other measures had failed. Hemorrhage was the actual cause of death, however, in six cases otherwise tabulated as abruptio placentae,² rupture of the uterus,³ and probable rupture of the uterus.¹ As much as eight units of plasma were given to one patient before blood was procured just prior to hysterectomy. In another case of postpartum hemorrhage bleeding continued for three hours in bed, while four units of plasma were administered; the uterus was continuously massaged, but not explored.

Hemorrhage was the actual cause of death in 35 per cent of the fifty-seven puerperal deaths. The following table will indicate the rubrics in which deaths due to hemorrhage were found (Table III).

TABLE III. HEMORRHAGE AS THE CAUSE OF MATERNAL DEATH (BROOKLYN, 1946)

| | OFFICIAL STATISTICS | HEMORRHAGE DEATHS |
|------------|------------------------|----------------------|
| Abortion | 7 | 4 |
| Ectopic | 2 | 2 |
| Hemorrhage | 8 | 8 |
| Toxemia | 12 | 1 |
| Infection | 12 | - |
| Accidents | 11 | 3 |
| Other | 5 | 2 |
| Total | 57 | 20 |

are but a means to an end. Actually, our purpose is to examine intensively obstetric experience in a large city. That this can be done in no way other than by review of case reports is clear. Our maternal death rate is at a new low level, yet the principal controllable factors are associated with the trauma of delivery.

We need more than case records of death. We need also an analysis of the nature of our lying-in institutions and better knowledge of their obstetric practice. It is not unjust to say that all too often plasma is held to be a satisfactory substitute for blood, and that adequate blood reserves are not maintained at all of our hospitals. Hemorrhage is still the principal cause of maternal death in Brooklyn. The red river is known to run through our city, yet its course and its tributaries elsewhere in the United States have not yet been charted.

During the last ten years, eighteen maternal deaths have been due to aspiration of vomitus during administration of anesthesia for delivery or shortly afterward. The number of aspiration asphyxia deaths for 1946 represents a new high for any one year. The danger of aspiration is not fully appreciated by many who practice obstetrics, and even the well-trained anesthetist may be unaware that the obstetric delivery, whether abdominal or pelvic, is not comparable to the elective surgery of the operating room. Repressed intrapartum fears often make induction troublesome, since self-control is abolished in this stage; and if induction is not smooth, the entire period of anesthesia may be stormy. Varying depth of anesthesia because of anxiety for the welfare of the baby, or significant delay just before induction is complete are equally dangerous.

The purpose of prenatal care is safe delivery; it is a waste of time if the danger signals set by pre-eclampsia and rheumatic heart disease are ignored. In either case, no matter when significant symptoms appear, there is no substitute for continuous hospitalization. And in either case, election of cesarean section as the method of delivery is not often wise.

For the last ten years approximately one-third of our maternal deaths, exclusive of those early in pregnancy, have been associated with cesarean section. Not only do its indications need close examination but a high standard of performance is required, with attention to every detail.

But safe conduct through any delivery requires no less of the obstetrician. Obstetric skill is not acquired without concern for every detail. No matter how simple, no two deliveries are just alike, even though spontaneous. Everyone who practices obstetrics must be aware of its hazards and make a studied effort to reduce or eliminate the number of deaths which might be called avoidable. By its very nature obstetrics is a sacred discipline.

Grateful acknowledgment is made to the Visiting Nurse Association of Brooklyn for invaluable clerical help.

Reference

1. Gordon, C. A.: Anesthesia as a Cause of Maternal Death. The I. C. Rubin Anniversary Number, J. Mt. Sinai Hosp., 1947.

CASE 6.—Age 38 years. Classical cesarean section under spinal anesthesia supplemented by nitrous oxide and ether. Great apprehension in the operating room and afterward. Fairly well for a few days except for moderate fever, pulse acceleration, and fear of impending death. On the sixth day her temperature was 104° F., pulse 140, and signs of consolidation were found in the lower lobe of the right lung.

CASE 7.—Age 36 years. Lower segment cesarean section under fractional spinal anesthesia was performed after thirty-six hours of labor. The patient was coughing a great deal the next day, when coarse râles were present over both lung fields, and diffuse opacity of the left lung base was reported by x-ray. Death on the sixth day with stertorous breathing, deepening cyanosis and very rapid pulse.

CASE 8.—Age 36 years. Lower segment cesarean section under gas, oxygen, ether sequence after thirty hours of labor. The next day fever was 102° F., pulse 144, and respirations 36. Cough was frequent and paroxysmal. Death on the following day was ascribed to pneumonia.

From 1937 to 1946, inclusive, fifty-one deaths from anesthesia have occurred in Brooklyn. Detailed report of forty-three cases prior to 1946 has been accepted for publication.¹

Rheumatic Heart Disease

Cardiac disease is of great importance. There were fourteen deaths due to this cause; nine were assigned directly to cardiac disease, and so not tabulated as maternal deaths; five were assigned to puerperal causes: Prenatal care was inadequate in all but two cases. In three cases cesarean section was performed—in one case just before death in a futile attempt to save the child, and in two cases under spinal anesthesia, which, it is likely, is contraindicated in cardiac disease. For brevity the essential data are set down in Table IV. The important deduction to be made is that hospitalization should be immediate and continue until term, once failure has occurred.

TABLE IV. DEATHS DUE TO RHEUMATIC HEART DISEASE ASSOCIATED WITH CHILDBIRTH, BROOKLYN, 1946

| STATISTICAL ASSIGNMENT | DURATION OF PREG-NANCY | DELIVERY | SIGNIFICANT DATA |
|------------------------|------------------------|------------------|---|
| Nonpuerperal | 6 months | Not delivered | Admitted in failure, death 3 days |
| Nonpuerperal | 6 months | Not delivered | Admitted in failure, death 4 hours |
| Nonpuerperal | 4 months | Not delivered | Died at home, failure previous delivery |
| Nonpuerperal | 8 months | Not delivered | Admitted in failure; death 1 day |
| Nonpuerperal | 36 weeks | Not delivered | Died at home; failure 2 months |
| Nonpuerperal | Term | Not delivered | Admitted in labor; death 10 hours |
| Nonpuerperal | Term | Not delivered | Admitted in labor; death 5 hours |
| Nonpuerperal | Term | Forceps | No anesthesia, long labor, death 12 hours later |
| Nonpuerperal | 28 weeks | Cesarean section | Decompensated; spinal, death 5 days |
| Infection | 32 weeks | Spontaneous | Short labor; no anesthesia, death 4 hours later |
| Infection | Term | Spontaneous | Short labor; no anesthesia, death 1 hour later |
| Infection | 32 weeks | Cesarean section | Decompensation; antemortem; local |
| Accidents | 40 weeks | Forceps | Admitted in failure, death 8 hours later |
| Accidents | Term | Cesarean section | Never decompensated; spinal |

Comment

It is quite a problem to present in manageable form the tremendous amount of material available to us. It is difficult to make numbers interesting. They

The length of the third stage in 157 cases (87.2 per cent) was up to five minutes. In 18 cases (10.0 per cent), it was between six to fifteen minutes, and in five cases (2.8 per cent) it was between sixteen to forty-one minutes.

TABLE I

| CASES | MINUTES | PERCENTAGE |
|-------|----------|------------|
| 157 | 0 to 5 | 87.2 |
| 18 | 6 to 15 | 10.0 |
| 5 | 16 to 41 | 2.8 |

Blood Loss in Third Stage

It is interesting to note that one-half of this series fell into the group where the blood loss ranged between 50 to 100 c.c. There were 90 cases, of which 40 were primiparas and 50 multiparas.

The next largest group numbered 56 patients (16 were primiparas and 40 multiparas) who lost up to 50 c.c. of blood. The third group of 27 patients (17 primiparas and 10 multiparas) lost between 110 to 450 c.c. of blood. The fourth group numbered seven, who lost over 450 c.c., and all of these were multiparas; two lost 450 c.c., four lost 500 c.c., and one lost 800 c.c.

TABLE II

| AMOUNT C.C. | PRIMIPARAS | | MULTIPARAS | |
|--------------|------------|----------|------------|----------|
| | NO. | PER CENT | NO. | PER CENT |
| 0 to 50 | 16 | 21.9 | 40 | 37.4 |
| 60 to 100 | 40 | 54.8 | 50 | 46.8 |
| 101 to 449 | 17 | 23.3 | 10 | 9.3 |
| 450 and over | 0 | 0.0 | 7 | 6.5 |
| Totals | 73 | 100.0 | 107 | 100.0 |

A brief review of three cases who lost more than 50 c.c. and less than 450 c.c. is presented:

CASE No. 21.—R. A., aged 26 years, para i. Pressure on admission 200/100, postpartum 76/66. Eclampsia with abruptio. Outlet forceps and episiotomy. Morbidity 99.2 to 100.0. Postpartum shock. Uterus five fingers above symphysis immediately post partum, and one fingerbreadth above symphysis on discharge. Placenta delivered with stillborn. Scant serous lochia throughout. No abdominal pain throughout. Measured blood loss third stage 200 c.c. The complicating toxemia and premature detachment of the placenta were, no doubt, responsible for the greater blood loss.

CASE No. 64.—C. B., aged 24 years, para i. Midforceps and episiotomy. Pressure on admission 100/62, after delivery 98/68. Placenta expressed after thirty-five minutes incarceration by cervix (removal spontaneous). No morbidity. Uterus six fingers above symphysis after delivery, and two fingers above on discharge. Slight pain (cramps) first day. Spotting after third day. Measured blood loss 200 c.c., probably a result of retained placenta.

CASE No. 82.—S. S., aged 34 years, para viii. Spontaneous delivery. Blood pressure on admission 130/92, after delivery 110/70. Retained, adherent placenta with manual removal. Uterus six fingers above symphysis after delivery, and two and one-half fingers on discharge. No morbidity. Spotting after third day. Slight cramps during first two days. Measured blood loss 100 c.c.

A PRELIMINARY REPORT ON THE CLINICAL USE OF METHERGINE

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THE intravenous use of oxytocic drugs has proved of great value in preventing and reducing obstetric hemorrhage. The present study was therefore undertaken in order to determine the effectiveness of Methergine, a synthetic ergonovine derivative. This substance was partially synthesized by Stoll and Hofmann, and subsequently studied pharmacologically by Kirchhof and his associates.

Previous clinical studies by Tollefson, Cartwright, and Rogers, Roberts, Hepp, and Evans, and Tritsch and Schneider have demonstrated Methergine to be a potent oxytocic as regards reduction of blood loss, shortening of the third stage of labor, and promotion of involution.

My objective in using this new synthetic drug, Methergine, was to observe its action on the postpartum uterus; the duration of the third stage; the amount of blood loss; postpartum pain; the character and amount of lochia; and finally to compare the amount of the drug necessary to obtain the same results as have been obtained with other oxytocics.

Procedure

In all of the 180 cases in this series, a 1 c.c. ampule of Methergine, containing 0.2 mg. of the drug, was given intravenously immediately after the birth of the child, and another 1 c.c. was given intramuscularly as soon as the placenta was delivered. Following the first intravenous injection, the uterus was massaged in order to attempt the expression of the placenta with the first hard contraction. This technique of manual expression, in my opinion, minimizes the blood loss and also the incidence of incarcerated placenta.

Following delivery, the first Methergine tablet (0.25 mg.) was given orally in about four to six hours, and repeated three times daily for two days unless more was thought necessary due to excessive bleeding. The latter was the exception rather than the rule.

From the birth of the child to the time when the patient was taken down from the stirrups, all the blood lost vaginally, including that from the episiotomy, was collected in a sterile basin, held below the buttocks, and measured.

Duration of the Third Stage

A short third stage was characteristic of this series. As a rule, the first contraction after the intravenous use of Methergine was exceptionally forceful. After expression of the placenta, the uterus became very hard and round, maintained this tone for several hours, and could be palpated more often in the midline than to one side. By the time the patient's legs were off the stirrups, there was usually only a slight trickle of blood from the vagina and, if the fundus of the uterus was held abdominally between the palms of both hands for fifteen to twenty minutes, this status quo lasted until the action of Methergine had worn off hours later.

The shortest third stage was one minute, with one exception, when the placenta was expressed with a stillborn fetus. The longest duration was forty-one minutes, giving a mean average of four and one-half minutes. The average length of the third stage in primiparas was 3.2 minutes, and in multiparas 4.6 minutes.

The three cetyl ammonium chloride compounds and ricinoleic acid stand out in their ability to kill all of the *Conidia*. The concentrations were chosen as current information indicates that they are within therapeutic range. Whether the methyl and butyl cetyl ammonium chloride compound may be used in stronger concentration or whether the diethyl compound would be equally as efficient in greater dilution has not been determined.

According to the conditions of this experiment, ricinoleic acid, cetyl dimethyl ammonium chloride, cetyl diethyl ammonium chloride, and cetyl (di-N-butyl) ammonium chloride hold promise as fungicides for monilia which produce vaginal mycosis. Clinical evaluations are now in progress, using 1 per cent concentrations of the cetyl ammonium chloride compounds.

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Blood Loss Over 450 Cubic Centimeters

CASE No. 4.—A. S., aged 31 years, para ii. Outlet forceps and episiotomy. Blood pressure 124/60 to 118/64. Membranes ruptured mechanically when fully dilated. Uterus atonic after five minutes at the end of the third stage, and second ampule of Methergine was given intramuscularly, followed by firm contraction with massage. No morbidity. Slight cramps on first day. Placenta delivered in three minutes. No flow on tenth day. Uterus six fingers above symphysis after delivery, and three fingers above on discharge. Blood loss 500 c.c. The reason for this amount of bleeding is obscure.

CASE No. 15.—A. M., aged 26 years, para iv. Blood pressure 112/78 to 120/82. Outlet forceps, no episiotomy. Gush of blood with birth of head. Several clots after expression of placenta in two minutes, and second ampule of Methergine was given intramuscularly. No morbidity. Uterus six fingers above symphysis after delivery and one and one-half fingers above on discharge. Cramps on first day. Scant spotting on tenth day. Blood loss measured 500 cubic centimeters.

CASE No. 59.—J. R., aged 24 years, para ii (Dr. M.F.G.). Outlet forceps, left episiotomy. Blood pressure 122/78. Placenta expressed in three minutes. No morbidity. No cramps. Very slight flow on discharge. Measured blood loss 500 c.c. probably due to bleeding vessel in episiotomy.

CASE No. 62.—E. M. L., aged 32 years, para iii (Dr. M.F.G.). Spontaneous delivery. Placenta expressed in four minutes. Two ampules Methergine given intravenously. Slight cramps first two days. No morbidity. No flow after third day. Uterus six fingers above symphysis after delivery, and three above on discharge. Measured blood loss 800 c.c., due in part to laceration through scar tissue.

Postpartum Pain and Lochia

About one-half the patients, more especially the multiparas, complained of slight cramps on the first postpartum day. These cramps started about fifteen to twenty minutes after receiving their first Methergine tablet, and lasted from one-half to two hours. No one complained of afterpains after the second day. Generally, postpartum pain was much less, and the uterus was less tender than when other oxytocics were used. Each day the size of the contracted uterus could be felt at a lower level, so that by the eighth postpartum day it could be palpated at between one to two fingerbreadths above the symphysis.

To date, there have been no postpartum hemorrhages in this series, nor has any woman had a "gush of blood" on getting out of bed. Eleven cases, or 5 per cent, had an elevation of temperature of 99.4° F. or more for two consecutive days. These could be further corrected if we take into consideration that elevation in temperature was connected with full and engorged breasts.

Except for occasional irregular spotting after leaving the hospital, most patients had a thin lochia, after the third or fourth day post partum, devoid of a foul odor. By the time of their six-week check-up the uterus was completely involuted. There was less complaint of low backache; the red cell count showed no more than a mild hypochromic anemia; and their general physical condition was good.

Summary

A series of 180 cases are presented in which a new synthetic drug, Methergine, was used.

The third stage of labor was appreciably shortened.

The blood loss in the third stage was decreased.

The prolonged action of the drug required less medication post partum. Postpartum bleeding and the amount of the lochia was decreased.

Involution took place sooner and the general condition of the patient was enhanced by its judicious use.

Conclusion

Methergine is a new synthetic oxytocic which seems to be very effective and safe when used in the third stage of labor.

I wish to express my thanks to Sandoz Chemical Works, Inc., who supplied both the ampules and tablets of Methergine used in this series. To the Sisters of Providence and the nurses at the Mercy Hospital, and to Dr. Milton F. Gipstein, I express my gratitude for their cooperation and help in collecting data.

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THE MENSTRUAL CYCLE LENGTH AND VARIABILITY OF YOUNG ADULT WOMEN

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AREY³ states that almost every aspect of human behavior has been quickly invaded by scientific curiosity, while the most obvious one of individual menstrual variability has been long neglected. Since recent investigations emphasize a definite time relationship between ovulation and menstruation, the length of the normal menstrual cycle has become more than a purely academic problem.¹¹ To anticipate the time of ovulation in a given individual, experimental results indicate that the typical length and variability of the menstrual cycle is of fundamental importance,^{2, 4} particularly when a specific test is to be employed.⁶ Menstruation consists of a highly complex physiologic mechanism, but the length and variability of the menstrual cycle may be easily determined. Careful detailed observations on the human menstrual cycle have been made, and the length and variability at certain age levels have been reported,^{3, 5, 7, 10, 13-19} but information concerning the pubescent and young adult is scant (Table I). To supplement the accumulated data, the present investigation was undertaken to determine the length and variation of the menstrual cycle in selected groups of late adolescent and young adult women.

TABLE I. COMPILATION OF DATA ON MENSTRUAL CYCLE LENGTH AND VARIABILITY

| SOURCE OF DATA | NUMBER OF SUBJECTS | SUBJECT AGE RANGE | MEAN AGE | TOTAL NO. CYCLES | CYCLE RANGE | MEAN LENGTH | STANDARD DEVIATION |
|-----------------------------|-----------------------|----------------------|----------|---------------------|----------------|----------------|-----------------------|
| Engle and Shelesnyak, 1934* | 100 | 11-15 | 13.1 | 3140 | 7-256 | 33.9 | 11.80 |
| Rork and Hellebrandt, 1940 | 231 | — | 15.5 | 1690 | 8-122 | 31.9 | 8.55 |
| Larsen | 17 | 16-20 | 17.5 | 130 | 6-61 | 28.88 | 7.11 |
| | 26 | 18-21 | 19.7 | 189 | 21-45 | 30.05 | 4.51 |
| | 22 | 18-21 | 20.2 | 147 | 21-47 | 29.86 | 4.19 |
| Fluhmann, 1934* | 76 | 18-27 | 20.4 | 747 | 11-144 | 30.4 | 11.58 |
| King, 1933* | 21 | 17-35 | 23.3 | 161 | 16-57 | 29.1 | 5.46 |
| 1926, 1933* | 33 | 17-35 | 23.8 | 716 | 18-53 | 27.7 | 3.68 |
| Scipiades, 1935* | 50 | 18-34 | 24.5 | 339 | 20-91 | 30.2 | 7.17 |
| Issmer, 1889* | 12 | 19-39 | 26.8 | 120 | 20-40 | 27.8 | 2.93 |
| Gunn et al, 1937* | 479 | 13-51 | 27.3 | 6000 | — | — | — |
| Latz and Reiner, 1935* | 102 | 20-45 | 31.0 | 1113 | 15-51 | 28.4 | 3.27 |
| 1937* | 100 | 21-49 | 31.7 | 1336 | 19-101 | 27.3 | 3.65 |

*Arey.³

Method

During one academic year each student subject kept a menstrual chart which followed a standardized method of recording data (Table II). The cycle lengths were then calculated, and the data analysed.

TABLE II. MENSTRUAL CYCLE RECORD CHART

| CYCLE DAYS | Menstruation | | | | | | | | | | Ovulation* | | | | | | | | | | | | | | | | | | | |
|------------|--------------|----|----|----|----|----|----|----|----|----|------------|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|--|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | |
| Dates | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| September | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 1 | 2 | 3 | 4 | 5 | 6 | | | |
| October | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 31 | | | | | |
| November | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | | | |
| November | 28 | 29 | 30 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | | | | |
| December | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 31 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | | | |
| January | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 31 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | | | | | | |
| February | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | |
| March | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 31 | 1 | 2 | 3 | 4 | 5 | | | | | | | |
| April | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 1 | 2 | 3 | | |

Subject: E. C.
Year: 1944-45
Birthday: January 18, 1924

Duration of bleeding: 5 to 7 days
Shortest cycle: 23 days
Longest cycle: 29 days
Average length: 26 days
Total number of cycles: 9

*Probable date of ovulation: 12th to 15th day of cycle.

Results

The subjects of the investigation were seventeen healthy freshmen women averaging 17.47 years of age, and two groups of twenty-six and twenty-two healthy junior women averaging 19.69 and 20.18 years of age.

The results of the freshmen records yielded 130 menstrual cycles ranging in length from 6 to 61 days, with a mean of 28.88 days, and a standard deviation of ± 7.11 days. The results of twenty-six junior records yielded 189 cycles ranging from 21 to 45 days in length, with a mean of 30.05 days, and a standard deviation of ± 4.51 days. The results of the group of twenty-two juniors yielded 147 cycles which ranged from 21 to 47 days, with a mean of 29.86 days and a standard deviation of ± 4.19 days (Table I). The junior data were taken during two different years, with remarkably similar results.

Discussion

It has long been a traditional medical teaching that normally menstruating women do so at regular intervals, demonstrating a 28-day spaced rhythm.^{1, 3, 7, 8, 10, 11} This viewpoint is still prevalent in some medical journals and modern textbooks,^{3, 7, 10} and it is often the custom to assume the normality of regularity as the basis of clinical questioning for case history purposes.^{1, 3}

Long ago it was stated by Fräenkel⁹ that the only regularity concerning the menses is their irregularity, and Hartman observed that the strictly regular woman is a *rara avis*.¹² According to Gunn, Jenkin, and Gunn the regular case is either an absolute myth, or is so rare as to be a medical curiosity,¹⁰ and Rossman and Bartelmez state that sufficient data support the conclusion that a recurrent 28-day cycle is an abstraction.²⁰ The results of this study are in accord with these conclusions. The cycle lengths were markedly variable, falling into three main groups of data: medium length cycles, very short, and unusually long ones. Of the total number of freshmen cycles the medium group comprised the majority of the cycles with lengths ranging from 18 to 41 days; four cycles were very short, 6, 8, 14, and 15 days, and four were unusually long, 55, 56, 57, and 61 days. Of the four individuals who experienced a brief cycle during the course of one academic year, only one individual also had an unusually long cycle. No attempt was made to obtain a diagnosis of the etiology of the extreme deviations from individual norms. However, in the instance of the very short cycle, followed by an unusually long one, this coincided with the initial experience of attending school away from home and undergoing the necessary adjustment to meet these new experiences. Two separate cases of unusually long cycles coincided with midterm examinations, which also suggest emotional stress as a possible disrupting factor.

The freshman cycle length ranged from 6 to 61 days, or a 55-day span, and the junior cycles ranged from 21 to 47 days, or a 26-day span. Thus the junior cycles exhibited a narrower range in length than the freshmen cycles, with the whole junior group falling into the medium cycle length group, skewed toward the high value. The shortest junior cycle was 21 days in length, and there were 6 long cycles in each junior group, 42, 43, 43, 44, 45, 45, and 40, 41, 42, 43, 43, and 47 days, but none to compare with the 61-day freshman cycle.

It has been reported that the menstrual rhythm of pubescent girls averaging 13.1 years of age ranges from 7 to 256 days,⁵ or a span of 249 days, and girls averaging 15.5 years range from 8 to 122 days,¹⁰ or a 114-day span (Table I). Thus, with increasing age the pubescent mean cycle length and its variability both tend to decrease.^{5, 10} The findings of the present study on the late adolescent are in accord with these conclusions. The freshmen women appear to have a shorter and less variable menstrual cycle than that of younger pubescent girls, and both groups of junior young women exhibit a similar decrease from that of pubescent girls as well as a narrowing of range in length as compared with the freshmen women (Table I). Maturity at the approximate age of 20 years apparently stabilizes cycle length and variability in young women.

Summary and Conclusions

Seventeen freshmen and forty-eight junior young women students, with ages averaging 17.47, 19.69 and 20.18 years, kept menstrual calendar records during one academic year. From these data the length and variability of menstrual cycles were calculated. The investigation yielded 466 menstrual cycles: 130 freshmen cycles ranging from 6 to 61 days in length, and 366 junior cycles ranging from 21 to 47 days in length; the freshman mean cycle length was 28.88 days, and the junior means 29.86 and 30.05 days; the standard deviation for freshmen was ± 7.11 and for junior ± 4.19 and ± 4.51 days.

The results support the following conclusions:

1. The mean cycle length in young adult women is longer than 28 days.
2. There is no significant difference between the mean cycle length of late adolescent and early adult women students.
3. There is an appreciable decrease in the variability of cycle length between late adolescent and early adult women students.
4. Increased maturity apparently exerts a stabilizing effect upon cycle length and variability in young adults.
5. There may be occasional large deviations from individual norms.
6. Arrhythmia of the menstrual cycle of healthy young women students appears to be a normal phenomenon.

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A NONSURGICAL METHOD OF THERAPY FOR CHRONIC ENDOCERVICITIS

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CHRONIC cervical infection is the most common lesion seen in gynecologic practice.¹ Fortunately, it is quite amenable to therapy in most instances, and rarely causes much concern to the patient or the doctor. In the treatment of sterility, degrees of cervical infection which would pass unnoticed in the average gynecologic patient may prove an annoying lesion and an efficient barrier to pregnancy. A method which has been found successful in our hands in the eradication of nonspecific endocervical infection is reported.

Materials and Methods

Twenty-five patients are included in this series. All but three were seen with the presenting complaint of sterility; these latter patients were seen because of a chronic discharge of many years' duration. Seventeen of the patients had never been pregnant to their knowledge; eight were parous. All disclaimed knowledge of gonorrheal infection, and the pelvic findings were within normal limits save for the cervical lesion to be described. Two had had therapy to the cervix for over five years, including repeated cauterizations and local therapy. The remainder had histories of short duration or had not noted serious leucorrhea.

The lesion considered in this paper is a definite clinical entity, although not necessarily bacteriologically or even pathologically specific. It is known as chronic endocervicitis and is characterized by the chronic and prolonged discharge of a heavy mucopurulent discharge from the external cervical os. This discharge is composed of mucous which is of high viscosity and opaque character, and, although it is usually at its most profuse stage just prior to and just following the menses, it is necessarily present and annoying throughout the whole cycle. The cervix may be lacerated or virginal, and there may or may not be an accompanying erosion.

Therapy was started only after the patient had been seen on two successive visits, one of which was in the "ovulation phase" of the cycle in order to be sure that the mucus did not become spontaneously clear at this time. At the second visit each patient was instructed to begin therapy three days following the date of onset of the following period. This therapy was as follows: one milligram of stilbestrol was to be taken by mouth daily for the next fifteen consecutive days; at the same time sulfadiazine, one gram three times daily, was to be taken by mouth for three days, and then the dosage was to be reduced to one-half gram three times daily for seven days. This would make a total of 15 mg. of stilbestrol in fifteen days and 19.5 Gm. of sulfadiazine in ten days. The endocervical mucus was re-examined in the "ovulatory phase" of the succeeding cycle, and if the improvement was marked, the stilbestrol was repeated the following month as before with omission of the sulfonamide. If there was no marked improvement, the complete course of stilbestrol and sulfadiazine was

resorted to the following month in the original dosages. Needless to say, if the mucus was water-clear and of low viscosity, therapy was entirely discontinued.

At the first visit the character of the cervical mucus was determined grossly. In almost all instances the mucus was too viscid to be aspirated with a syringe. After therapy, improvement was determined by the gross cloudiness of the layer on a slide over a dark background and by microscopic inspection. Specimens were considered completely satisfactory when the mucus was microscopically free of leucocytes and the viscosity approximated that of saliva.

Results

Results of therapy of twenty-five patients are shown in Table I. In only one case could treatment be considered a complete failure, and here the cervical mucus became of low enough viscosity to aspirate with a syringe, but never clear or significantly reduced in volume. Treatment was continued over twelve months, the prescribed course of therapy being repeated four times. It is of interest that this patient had had this condition for over twelve years, had had a conization of the cervix, several types of cautery applied, and had been advised to have a cervical amputation.

Three patients could not be considered cured, although they improved to the point of clinical disappearance of the mucoid discharge. It was never possible to obtain water-clear mucus of low viscosity, and recurrence of the original condition following cessation of therapy was noted in one of these patients.

Twenty-one of the patients became cured of the cervical discharge so far as could be determined clinically; microscopic visualization of the mucus showed no pus cells. The viscosity was that approximating saliva.

TABLE I. A SUMMARY OF THE RESULTS OF THERAPY OF TWENTY-FIVE PATIENTS WITH CHRONIC ENDOCERVICITIS

| | CASES | CURED | IMPROVED | NO CHANGE |
|-------------|-------|-------|----------|-----------|
| Nulliparous | 17 | 14 | 2 | 1 |
| Parous | 8 | 7 | 1 | 0 |
| Total | 25 | 21 | 3 | 1 |

Discussion

The rationale of this type of therapy is thought to be a combination of estrogenic enhancement of the resistance of the cervical mucosa with stimulation of overgrowth² and the antibacterial effect of the sulfonamide drug. Why the body itself has been unable to clear up this low grade infection in most instances is not clear, since all these patients were shown to have been ovulating with reasonable frequency and therefore presumably were maintaining normal estrogen levels.

The effect of ovulation on the amount and viscosity of the cervical mucous has been extensively investigated,³ and the use of estrogens in lowering viscosity in sterility patients in whom the cervical mucous may be acting as a barrier is considered rational.

The use of sulfonamides locally in the therapy of cervicitis and vaginitis is widespread and the therapeutic advantages are unquestioned.⁴ For lesions of the endocervix, little benefit could be expected because of the improbability of contact with the infected gland bases. The systemic use of the chemo-

therapeutic agent invalidates this objection, as in the therapy of low grade urinary tract infections, small dosages seem to be adequate. This is fortunate since one is usually not justified in giving potentially harmful amounts of this drug to ambulatory patients.

Unwonted reactions such as nausea and disturbance of the menstrual cycle were noted in over one-half of the patients, but rarely necessitated discontinuance of therapy.

This series is of necessity small, but the number of absolute failures seems to render it significant. In view of the simplicity and harmlessness of the medication, it would seem to be a logical step to take even in the preparation of the patient who may later need cauterization. If further investigation bears out these results, much cauterization and the resultant inconvenient and even harmful effects of this means of therapy may be obviated.

Sensitivity to either drug employed is obviously a contraindication to this type of therapy.

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THE USE OF GELATIN FOAM SPONGES IN OBSTETRICS AND GYNECOLOGY

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THE various properties of the recently introduced gelatin foam absorbable sponges have been thoroughly investigated,^{1, 2} but their principal clinical application to date has been in the realm of neurosurgery.^{3, 4} During the past nine months we have employed these sponges extensively on the gynecologic service of The University and St. Francis Hospitals* in an effort to evaluate their proper clinical application in obstetric and gynecologic surgery.

In their dry state the sponges are crisp, moderately friable wafers. They are moistened by immersing in the desired solution and gently compressing until all air bubbles have been expressed, after which they may be dried by pressing them on gauze pads. The term "sponge" has apparently been prompted by analogy in physical appearance and does not apply to their function. Gelatin foam sponges are not intended entirely to replace gauze sponges at the operating table. Moistened with either saline or a solution of bovine thrombin, however, they provide a valuable means of hemostasis.

In ten patients, purely for experimental purposes, portions of sponge were left in the uterine cavity at the time of curettage. As evidenced by the somewhat malodorous discharge, degeneration began within forty-eight hours and persisted for about ten days. Apparently most of the sponge was lost by discharge rather than by absorption.

The intrauterine use of these sponges, however, is hazardous, and requires an understanding of the mechanism of intrauterine hemostasis. Neither postpartum blood nor menstrual blood is a clotting fraction,⁵ and in vitro experiments in this laboratory have indicated that a sponge saturated with thrombin will not cause clotting of these bloods. In this respect they differ sharply from both oxalated and heparinized blood which we have found will clot in vitro after the addition of a portion of thrombin moistened sponge. It must be remembered, therefore, that the use of these sponges to control postpartum bleeding or excessive menstrual flow is without physiologic foundation. There is, indeed, no indication that the formation of a clot in the uterine cavity plays any part in the control of uterine bleeding,⁶ and during the postpartum period intrauterine sponges would have the additional potential hazard of preventing adequate contraction of the sinuses of the placental bed.

Perineal and abdominal surgery.—The use of these sponges for hemostatic purposes in both perineal and abdominal surgery has provided us with an

*The gelatin sponges used were generously supplied by the Upjohn Company, who market them as Gelfoam.

An apparatus has been devised that permits the safe introduction of small amounts of carbon dioxide by fingertip regulation. The instrument is equipped to measure the intra-abdominal negative pressure in cubic centimeters of water.

Occasionally, tubal patency can be determined without resorting to positive intrauterine pressure. A negative intra-abdominal pressure of 15 to 30 cubic centimeters of water is created by assumption of the knee-chest position. Subphrenic air will occasionally occur when a cervical cannula is introduced in this posture. Such an occurrence is indicative of normal patent, nonspastic tubes. The ability to measure intra-abdominal negative pressure through the cervical cannula is positive proof of tubal patency and, at the same time, avoids the necessity of introducing intra-abdominal gas. Intratubal trauma is avoided, and there is no postexamination distress. The author now uses this procedure as a screening process before applying positive pressure.

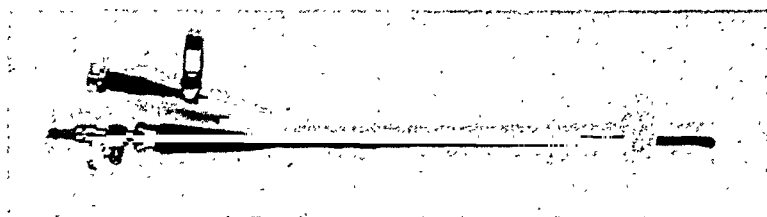


Fig. 2.—Cannula with self-retaining bag inflated.

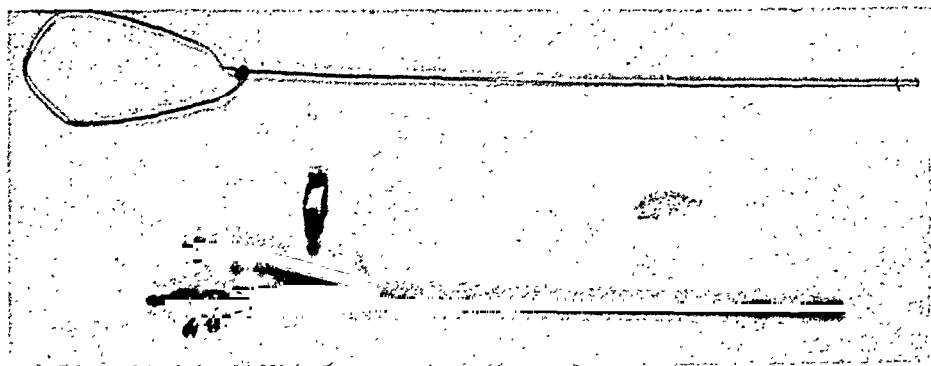


Fig. 3.—A, Metal stylet used to introduce the cannula. B, The self-retaining cervical cannula with bag deflated. Attachment for bulb or syringe to deflate the bag is shown, also attachment for tubing from the salpingometer.

The instrument consists of a small metal box 7 by 6 by 5½ inches and, when opened, presents two manometers for measuring positive pressure in millimeters of mercury and negative pressure in cubic centimeters of water. Below the meters there are two hand knobs. One serves as a pump and is connected with the intake and output tubes, while the other is the selector to direct the flow of carbon dioxide in different desired routes through the instrument. The output tube is attached to a length of rubber tubing, and the input tube is attached to a bag previously filled with 100 to 300 cubic centimeters of carbon dioxide. When the rubber tubing from the salpingometer is attached to the self-retaining cannula, the carbon dioxide is introduced five cubic centimeters at a time by slowly turning the pump knob in the manner usually employed in winding a watch. The intrauterine pressure attained at all times is indicated in millimeters of mercury on the positive pressure manometer. The author also employs a monaural stethoscope over the lower abdomen to hear the air escape from the tube. With one ear free, it is easier to differentiate sounds caused by intraperitoneal gas and the gas escaping at the cervix.

SALPINGOMETER AND SELF-RETAINING CANNULA FOR TESTING TUBAL PATENCY

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THE tubal patency test is being performed in many clinics by means of improvised apparatus. Frequently the apparatus is uncommendable, if not actually dangerous. The danger lies in the fact that air is frequently used as the insufflation medium, and is often introduced by means of a rubber bulb or syringe. No safeguards are employed against the sudden and inadvertent introduction of large amounts of air under pressure that exceeds the safe limit.

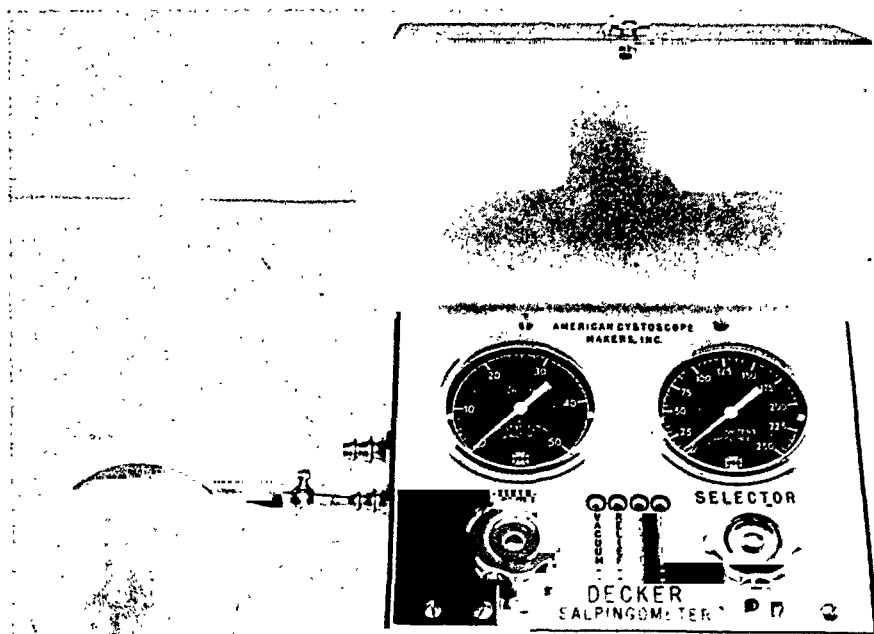


Fig. 1.—The Decker salpingometer with CO₂ container attached to inlet tube.

The introduction of air under pressure into the uterine cavity can result in fatal embolism. Carbon dioxide emboli have never been reported. Air should never be used as a medium for tubal insufflation.

The Rubin test is now widely employed. With the occasional investigator of female infertility, it is frequently the first and only diagnostic procedure employed. There is need for a safe and convenient apparatus.

A NEW ENDOMETRIAL BIOPSY CURETTE

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THE gynecologist who does any volume of microscopic endometrial studies, and is forced by necessity to use the endometrial curettes now on the market, cannot help but be impressed with the difficulty and awkwardness entailed in their usage.

The more simple the task in obtaining curettings, and the ease with which the specimens can be obtained, the more often the gynecologist will include this valuable adjunct to his armamentarium of diagnostic procedures.

The endometrial curettes now on the market include the standard type loop uterine curette and the biopsy suction curette with its various modifications.

The loop curette is not satisfactory for office biopsies due to its size and the difficulty in evacuating the curettings from the uterus when seeking only small amounts of tissue.



Fig. 1.

The suction curette, although small, has the disadvantage of being of rigid construction and not adaptable to all variations in directional contours of the endometrial cavity. Likewise, whether the suction feature of the curette is used or not, it requires the curettings to sweep up into the hollow shank of the handle, which is a direction they follow with difficulty unless suction is applied.

The endometrial biopsy curette here described has in my hands eliminated the undesirable features of the suction curette. Because of its simplicity, and the ease with which specimens can be obtained, it appears to be superior to other curettes.

The curette consists of a head which contains a steel cutting edge similar to the sharp loop curette. Just below and distal to this cutting edge is a hollow trap to retain the detached endometrium. The cutting head has an over-all transverse diameter of $\frac{3}{16}$ inch, and the trap inside measures $\frac{3}{16}$ inch by $\frac{3}{16}$ inch. This gives a fairly satisfactory sized piece of tissue with only one sweep of the instrument. The distal end of the shaft adjacent to the cutting head is of soft malleable brass which can be molded to fit any type of contour. This ability to shape the shaft adds greatly to its efficiency. Likewise, the larger four-sided handle makes the ease of handling the instrument much superior to that of the suction curette.

Fig. 1 illustrates the cutting head and trap of the curette.

The principle of the Foley catheter has been adapted to the cervical cannula.* The cannula consists of a catheterlike rubber tube with a small inflatable rubber bag integral with the outer wall of the tube near the tip. The cannula is introduced by means of a stylet which can be molded to any direction of the cervical canal. When the inflatable rubber bag is beyond the internal os, it is inflated with 3 to 5 cubic centimeters of air and the stylet removed. The cannula remains in place when properly introduced and can be manipulated with ease without the use of a tenaculum on the cervix. Inflation of the bag within the canal diminishes its self-retaining property and is more painful. The cannula is particularly useful when it is desired to change the position of the patient to the lateral, prone, or knee-chest.

Method of Examination

The instrument is placed on a table beside the examiner. The carbon dioxide bag is partially filled with gas and attached to the input tube. The length of rubber tubing is attached to the output tube. The stylet is placed within the cannula and it is slipped through the cervix until the bag is beyond the internal os. The bag is then inflated and the stylet removed. The cannula is clamped near the end and the patient changed to the knee-chest position. The rubber tubing is attached to the cannula, and the selector moved to vacuum. The clamp on the cannula is then removed. Small changes in the negative pressure are usually due to a vacuum within the tube. Readings of 10 to 15 cubic centimeters of water are indicative of normal, nonspastic tubes, and further examination is unnecessary. Tests with positive pressure can be made in the dorsal or the knee-chest position.

In the event that negative pressure is not noted, the selector is moved to output (positive pressure) and the pump knob is turned slowly in the manner of winding a watch and the positive pressure noted on the manometer.

Summary

An instrument to test tubal patency has been described that makes use of intra-abdominal negative pressure and positive pressure with a carbon dioxide medium.

A self-retaining, intrauterine cannula employing the Foley catheter principle has been described.

*The American Cystoscope Makers, Inc., New York, who manufacture the Foley catheter, also make the cannula.

centuries used such symbols as " π " and " π^2 " with notable success. History-taking in gynecology and obstetrics might similarly gain by the use of such a system. This is not at all entirely new to gynobtries.* Thus the Roman symbols for Mars and Venus have long been used for denoting the male (σ) and the female (φ).

The important gynecologic and obstetric signs and symptoms can be broken down to a relatively small number, and translated into symbol form (Fig. 1). These symbols can be projected in sequence on a life graph, which may aptly be called a "vita-gynograph."

"Gynographies" have the following advantages: (a) speed of recording; (b) speed of interpretation; (c) conciseness, clarity, and comprehensiveness; (d) signs and symptoms in sequence at a glance; (e) universal language.

The author wishes to thank Faith Hope Kahn, R.N., for her painstaking assistance in the experimental phases of the translation of many actual case histories into "vita-gynograph" form.

Reference

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*"Gynobtric": pertaining to gynecology and obstetrics. ("gynobtrician": one who practices gynecology and obstetrics.)

GYNOGRAPHICS

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GYNOGRAPHICS may be defined as "symbolism in obstetrics and gynecology."

The use of symbols is an old custom in the history book of mankind. Thus, the astronomers, the botanists, and the chemists have long availed themselves of a system of signs¹ for the purposes of brevity and lucidity. Physicists have long used the symbol "M" for mass. Mathematicians have for






























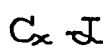










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|--|---|--|---|---|-------------------------------|
| V A G I N A L B L E E D I N G |  | VAGINAL BLEEDING | B R E A S T |  | BLEEDING FROM BREAST |
| |  | MENSTRUATION (<i>for 3 days every 28 days</i>) | |  | MASS IN BREAST |
| |  | MENORRHAGIA | B L A D D E R |  | URINARY FREQUENCY 8 X 24 HRS. |
| |  | CESSATION OF VAGINAL BLEEDING | |  | DYSURIA |
| |  | VAGINAL BLEEDING WITH CLOTS | | | |
| |  | VAGINAL SPOTTING | | | |
| |  | METRRHAGIA | | | |
| V A G I N A L D I S C H A R G E |  | IRREGULAR VAGINAL BLEEDING | P A I N |  | RU.Q. PAIN |
| |  | VAGINAL DISCHARGE | |  | LL.Q. PAIN |
| |  | CESSATION OF VAGINAL DISCH. | |  | DYSMENORRHEA |
| P R E G N A N C I E S |  | VAGINAL BLEEDING & DISCHARGE | |  | INCREASING DYSMENORRHEA |
| | | | |  | DYSPAREUNIA |
| |  | FULL TERM NORMAL MALE | S U P P L E M E N T A R Y |  | MASS IN I.U.Q. |
| |  | FULL TERM NORMAL FEMALE | |  | COITUS |
| |  | FULL TERM FEMALE STILLBIRTH | |  | PHYSICAL EXAM. |
| |  | FULL TERM MALE STILLBIRTH | |  | PRESCRIPTION |
| |  | TWINS , TRIPLETS , ETC. | |  | CERVIX , INJECTION |
| |  | TUBAL PREGNANCY | |  | LESION OF CERVIX |
| |  | { SPONT. ABORTION AT 3 MONTHS <i>Drops = Number of Months</i> | |  | LESION OF VULVA |
| |  | { INDUCED ABORTION AT 3 MONTHS <i>= 3 Months</i> | |  | DIAGNOSTIC CURETTAGE |
| |  | { THERAP. ABORTION AT 2 MONTHS <i>= 2 Months</i> | |  | ANY DESCRIPTION NOT COVERED |
| |  | INCOMP. ABORTION AT 3 MONTHS | |  | RADIO THERAPY , COLPOTOMY. |

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instrument of considerable value. The raw oozing surface in the posterior cul-de-sac following the dissection out of endometriosis or old inflammatory diseases is particularly amenable to such management, and we have also employed them following the stripping of the bladder flap from the uterus.

In the postoperative courses of these patients we have noted no febrile reaction of significance which could be ascribed to the absorption of the sponge. On subsequent examinations, no undue scar tissue could be palpated which could be attributed to their absorption. From such follow-up examinations, however, it was our impression that the disappearance of the gelatin was much more rapid than has been reported in the animal, beginning within a day or two after surgery and being complete within one or two weeks. One patient in this series was readmitted four weeks after hysterectomy for emergency surgery of the upper abdomen, and exploration of the pelvis at that time revealed good healing with no evidence of residual from the previously employed (9 cm. by 13 cm.) sponge. In another patient with an inoperable malignant cyst of the ovary, marsupialization was employed, providing us with an opportunity to follow the fate of the sponge left in the cyst cavity. Absorption began shortly after operation, and was complete two weeks later.

From the point of view of hemostasis, it cannot be stressed too frequently that these sponges with anticoagulants do not constitute an alternative to the hemostat. Their fields of application are quite distinct, and to substitute the absorbable sponges for the hemostat or ligature will create far more problems than it will solve. At the operating table we have not been able to observe any great difference in speed of hemostatic effect with or without the bovine thrombin. The gelatin sponges themselves, when saturated in blood or saline, apparently have a coagulative action, and we feel that their proper use is as important as the solution used. The careful pressing out of all air bubbles from the material at the time of moistening, and the maintenance of firm pressure to the sponge for a few minutes after applying it to the tissues are the steps of greatest value in obtaining hemostasis.

Comparative bacteriologic studies in this laboratory indicate that the gelatin can serve as a culture media for organisms. The sponge saturated with blood, however, does not constitute a culture media significantly more favorable than does clotted blood alone, and the hazard is more potential than real.

It has not yet been demonstrated that a raw area covered by an absorbable gelatin sponge corresponds surgically to a peritonealized area. Nevertheless, in about a third of the laparotomies in which they were employed in the posterior cul-de-sac, no peritonealization was carried out. Until further investigations are reported, however, gelatin foam sponges should be used as a substitute for peritonealization with great caution, and only when more standard methods cannot be employed.

Conclusions

1. The use of absorbable gelatin foam sponges in obstetric and gynecologic surgery has been reviewed.

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SICKLE CELL ANEMIA AND PREGNANCY

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THE infrequency of pregnancy in women with sickle cell anemia is suggested by the fact that to date only 20 cases have been reported.¹⁻¹³ This is surprising when, by survey, it is noted that about 8 per cent of Negroes in the United States¹⁴ have the "trait"; that is, they have erythrocytes which are capable of assuming the "sickle" shape; and about 0.2 per cent of Negroes^{14a} have, in addition, the clinical entity called sickle cell anemia. This is manifest by episodes of pain in various parts of the body, fever, jaundice, hepatomegaly, chronic ulcers of the extremities, persistent anemia with sickled and nucleated erythrocytes in the peripheral blood, leucocytosis, reticulocytosis and a hyperplastic bone marrow.

Cases of sickle cell anemia and pregnancy may frequently be overlooked clinically, and, for this reason, three additional cases are here reported. Two of these patients had signs and symptoms of central nervous system involvement which occurred immediately following delivery and presented a picture resembling toxemia of pregnancy.

Case Reports

CASE 1.*—B. L., a 23-year-old Negro woman, was admitted to the hospital on Sept. 26, 1944, because of amenorrhea since April 23, 1944, and anemia. She had a history of "pneumonia" recurring since the age of 8 years and occasional attacks of abdominal pain, fever, and chills, with jaundice. On several occasions these attacks were accompanied by periods of unconsciousness. She was short, slight of stature, icteric, and pale. The blood pressure was 90/50. There was a soft apical systolic murmur and an accentuated pulmonic second sound. The uterus was symmetrically enlarged to the level of the umbilicus, and there was slight pitting edema of the ankles.

Laboratory Findings on Admission.—Urinalysis—albumin, 4 plus; occasional granular casts and erythrocytes. Blood count—hemoglobin, 4 Gm. (or 26 per cent); erythrocytes, 1,380,000 per cu.mm.; reticulocytes, 0.8 per cent; platelets, 442,000; leucocytes 11,500; differential count, normal. Nucleated and sickled erythrocytes were present in the blood smear. The erythrocyte fragility tests showed increased resistance. There was hyperplasia of the erythroid elements of the bone marrow. The urea clearance was 40 per cent, with a blood urea nitrogen of 20 mg. per cent. The urine urobilinogen was positive in a dilution of 1 to 100. Roentgenograms showed a thinning of the cortexes of the bones, the heart appeared enlarged in all diameters, and the lung markings were generally increased in intensity.

*The Charlotte Drake Cardeza Foundation performed many of the hematological studies recorded for Cases 1 and 2.

2. The intrauterine use of such sponges with or without thrombin solution for hemostatic purposes is without physiologic basis, and in menstrual or post-partum bleeding is potentially hazardous.

3. The sponges provide an excellent means of hemostasis in the control of oozing areas in pelvic or perineal surgery, whether used with thrombin or with saline. They supplement, but cannot replace, the hemostat.

4. Neither a febrile reaction nor excessive scar formation has been noted in the postoperative course of these patients.

5. The gelatin-foam sponge impregnated with blood provides a potential culture media for bacteria, but not significantly different from that provided by clotted blood.

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minutes later. The uterus contracted well. During the postpartum period of hospitalization the patient's temperature varied between 99° and 100° F., without evidence of infection.

On Oct. 21, 1942, the patient returned, complaining of nausea, dizziness, shortness of breath, blurred vision, palpitation, and continuous abdominal pain. She was pregnant, and the estimated date of delivery was Jan. 8, 1943. Two months later she had a sudden sharp pain in the left hemithorax associated with dyspnea, cough, and white mucoid expectoration. The symptoms gradually subsided with bedrest.

On Jan. 5, 1943, after a labor of fifteen hours, the patient spontaneously delivered a premature-appearing female child (child 3). The following day the patient developed dyspnea, severe pain in the left side of the chest, accompanied by cough and mucoid expectoration. In addition she complained of severe pain in the left leg. The scleras were icteric. There were signs of atelectasis on the left side of the chest posteriorly. The liver edge was two inches below the right costal margin. The sputum showed the usual respiratory organisms (culture) with a negative smear and culture for tubercle bacilli. Leucocytes numbered 53,000 with a normal differential count, but 870 nucleated erythrocytes were counted for each hundred leucocytes. Reticuloocytes averaged 40 per cent. The van den Bergh reaction was positive direct with the serum bilirubin 1.5 mg. per cent. A roentgenogram showed cardiac enlargement with an increased density in the lower left lung field. The impression of the hematologist, Dr. L. M. Tocantins, was that the patient had sickle cell anemia with pulmonary infarction. She was discharged, improved, on Jan. 30, 1943.

Children.—

Child 1: At 8 years of age this child had a hypochromic anemia but no evidence of sickling.

Child 2: At 6 years of age examination of the blood showed a normal erythrocyte count with a low color index but no evidence of sickling.

Child 3: At 3 years of age examination of the blood revealed a low color index with sickling present.

(The case histories of these children are to be published in detail, elsewhere.)

CASE 3.—E. W., a 22-year-old primipara, was admitted to the hospital July 10, 1946, because of painful, slightly swollen joints of the extremities. She gave a history of similar attacks occurring about once a year since the age of 12 years. There were systolic murmurs at both the pulmonic and mitral regions of the heart. The blood pressure was 94/52. The uterus was enlarged to about the size of a six months' pregnancy.

Laboratory Findings.—Urinalysis negative. Blood count—hemoglobin, 5 Gm. (or 33 per cent); erythrocytes, 1,890,000 per cu.mm.; leucocytes, 12,000; polymorphonuclear cells, 73 per cent; eosinophiles, 2 per cent; lymphocytes, 20 per cent; monocytes, 7 per cent; and nucleated erythrocytes, 36 per hundred leucocytes counted. Sick cells were present in the ordinary blood smear. Reticuloocytes were 1 per cent. The bone marrow showed an increase in erythropoietic elements. There was 5 per cent retention of bromsulfalein, the van den Bergh reaction was positive direct, and the serum bilirubin was 1.1 mg. per cent with the urine urobilinogen positive in dilution of 1 to 50. The blood urea nitrogen was 8.8 mg. per cent; the urea clearance, 85 per cent; the serum uric acid, 5.8 mg. per cent. Roentgenogram of the chest showed cardiac enlargement, particularly of the left ventricle.

The patient was discharged after receiving three transfusions each containing 500 c.c. of citrated blood, and was readmitted on Sept. 16, 1946, in labor about two weeks before the estimated date of delivery. The erythrocyte count

During the next three months the patient received five transfusions of citrated blood, 500 c.c. each, and four transfusions of red cell suspension, 600 c.c. each. The edema of the ankles increased, and the blood pressure rose to 152/92. The membranes ruptured spontaneously on Jan. 22, 1945, after thirty-nine hours of labor. The patient immediately delivered herself of a cyanotic, 3 pound, 12 ounce male infant. After spontaneous delivery of the placenta she complained of headache. The blood pressure was 140/110. She was given 0.01 Gm. of morphine sulfate, subcutaneously. Four hours post partum she had convulsions during which she fell from bed, became unconscious, and was incontinent of urine. Convulsions recurred an hour and one-half later. The retinal veins were distended; the arms and legs were spastic; Babinski's sign was present bilaterally. A spinal fluid study was normal. The impression of the neurosurgical consultant (Dr. Rudolph Jaeger) was "... diffuse brain irritation by multiple lesions, probably petechial hemorrhages. . . ." On the following day the blood urea nitrogen was 30 mg. per cent, and the serum uric acid 8.8 mg. per cent. She gradually regained consciousness until on the fourth day she was able to read and write. A week after the convulsions she was free of abnormal neurologic findings, except for involuntary muscular twitches of the face, arms, or legs occurring several times each hour, frequent headaches, and a "hazy memory." The serum uric acid declined to 4 per cent, and the urea clearance to 16 per cent. The electroencephalogram was abnormal, nonspecific type. A year later the electroencephalogram was normal.

The baby fed poorly and died eleven days after birth. Blood counts, platelets, and fragility tests were normal. At no time was sickling present. Autopsy revealed prematurity, subarachnoid hemorrhage, and aspiration pneumonia.

The erythrocytes of the child's father showed no sickling.

CASE 2.—S. M., a 21-year-old Negro woman, was admitted to the hospital Jan. 17, 1940, with amnorrhea since Sept. 20, 1939, a genital sore, and vaginal discharge for three weeks, lower abdominal pains for six days. There was a scar over the left tibia from a chronic ulcer in childhood. On March 9, 1938, she had had an uncomplicated delivery of her first child, a girl (child 1). The blood pressure was 100/60. There was a systolic murmur at the aortic region of the heart. The entire right side of the abdomen was tender, and the uterus was symmetrically enlarged to the level of the umbilicus.

Laboratory Findings.—Urinalysis—albumin, 1 plus (noncatheterized). Blood count—hemoglobin, 6.9 Gm. (or 45 per cent); erythrocytes 2,770,000 per cu.mm.; leucocytes 8,300 with a normal differential count. There were, however, 547 nucleated erythrocytes to each hundred leucocytes in the blood smear which also contained occasional sickled erythrocytes. The bone marrow showed hyperplasia, especially of the erythroid elements. Cervical and urethral smears were negative for gram-negative intracellular diplococci. The Frei test was negative. The blood Wassermann and Kahn tests were plus 4. A roentgenogram of the chest showed a generalized intensification of the pulmonary markings and enlargement of the cardiac silhouette.

The patient's temperature returned to normal in three days. She complained of pain in the bones of the extremities, and it was noted for the first time that the liver was enlarged. After her discharge from the hospital she received antisyphilitic therapy (bismuth and iodides). Up until the time of delivery she complained of dizziness, blurred vision, nausea, dyspnea, and palpitation. The ankles were edematous.

The onset of labor was at 8:45 P.M. on May 24. The blood pressure was 112/80. Approximately one and one-half hours later she delivered, spontaneously, a 6 pound, 4 ounce female child (child 2). The placenta delivered, intact, ten

function, edema of the lower extremities, hypertension, increased serum uric acid, convulsions, and a comatose state; these findings, together with the fact that the patient was a primigravida, strongly suggested that she had eclampsia. It must be noted, however, that she had periods of unconsciousness previous to her pregnancy, apparently as a part of a state of "crisis." In 1940 Hughes, Diggs, and Gillespie¹⁵ described six cases of involvement of the nervous system in sickle cell anemia and reviewed twenty-five cases from the literature. Drowsiness, stupor, or coma occurred in sixteen of these, hemiplegia in fourteen, and convulsions in eight. If this patient had a "crisis" as a complication of her pregnancy, clinical evidence suggests that it involved only the central nervous system. This, too, has been reported. These same authors and Connell¹⁶ have described the presence of thrombi, areas of necrosis, hemorrhage, pigmentation, and vascular intimal proliferation in the brain in sickle cell anemia. Our patient had normal cerebrospinal fluid. In their cases the state of the cerebrospinal fluid was variable and often normal, even in the presence of diffuse cerebral involvement.

In Case 3 hypertension developed within twelve hours post partum, accompanied by blurring of vision, nuchal rigidity, a bilaterally positive Kernig's sign, and elevation of the serum uric acid. Later there were signs suggesting a lesion of or near the circle of Willis. The evidence presented in both Case 1 and Case 3 suggested the presence of cerebral thromboses, hemorrhages, or both.

Both patients of Case 1 and Case 3 had rather acutely declining urea clearance values associated with pregnancy and elevated values for serum uric acid during the period with hypertension and abnormal cerebral signs. According to Dexter and Weiss,¹⁷ a declining urea clearance value is not common in normal pregnancy, but is frequently seen in toxemia. The studies of Schaffer, Dill, and Cadden¹⁸ suggest that the increased uric acid content of the blood in toxemia is due to a decreased renal clearance of uric acid, and postulate that there is not a concomitant rise in urea nitrogen because pregnancy normally lowers the blood urea content. Renal impairment and even uremia may occur in sickle cell anemia.¹⁹

The evidence strongly suggests that toxemia was present in Cases 1 and 3. In toxemia of pregnancy it is generally accepted that there is spasm of the arterioles.²⁰ This spasm superimposed on vessels already partially occluded by intimal proliferation may bear an important relationship to the occurrence of signs and symptoms of cerebral vascular blockage.

In Case 2 there was evidence of pulmonary infarction as a complication of pregnancy. Six of the patients previously reported had symptoms and signs, during their pregnancy, which were suggestive of pulmonary infarction. In all three cases there were complications by vascular phenomena, probably thromboses. This is a characteristic of sickle cell anemia, but in these instances it would appear that the tendency, was, in some manner, enhanced by pregnancy.

Summary

1. Three case reports of sickle cell anemia in pregnancy are added to the twenty published cases.

was 2,500,000 per cu.mm. She received 500 c.c. of citrated blood during labor. The membranes were artificially ruptured and, under spinal anesthesia (50 mg. novocain), a 4 pound, 4½ ounce living male child was delivered by forceps after a labor of about 24 hours. During the prenatal period the highest level recorded for the blood pressure was 134/74. About twelve hours post partum the patient started to complain of severe frontal headache and blurring of vision. The blood pressure at this time was 180/100. The following day it was noted that there was nuchal rigidity, bilaterally positive Kernig's sign, and generalized hyporeflexia. The serum uric acid was 8.8 mg. per cent; serum bilirubin, 1.1 mg. per cent. On the third day post partum the spinal fluid pressure was 470 mm. of water; 22 c.c. of yellow fluid were removed, the analysis of which showed many erythrocytes; sugar, 50 mg. per cent; protein, 30 mg. per cent; Wassermann, negative; and absence of growth on culture.

The patient developed transitory ptosis of the right eyelid with limitation of internal and upward movement of the eyeball and Cheyne-Stokes type of respiration; papilledema was present bilaterally. The liver was enlarged and tender, and the spinal fluid pressure remained elevated. Very slow reduction of this pressure gave much relief from the headache, and the respirations became more regular. At no time did the blood urea nitrogen go above 11 mg. per cent, but six days post partum the urea clearance was 50 per cent. The serum uric acid decreased to 4 mg. per cent. A month post partum the cerebrospinal fluid was normal except for a pressure of 400 mm. of water. By Oct. 20, 1946, there was sufficient clinical improvement to permit the patient to be discharged to the Out-Patient Department.

An electroencephalogram performed at the first admission was normal. One performed ten days post partum was abnormal, but had no definite localizing criteria.

The general progress of the baby was good. Blood counts performed from within twenty-four hours of birth to four weeks of age were normal. Stasis moist preparations made at about 3-day intervals showed sickling for the first time on the twenty-fourth day.

Discussion

These three patients had the typical signs and symptoms of sickle cell anemia. A critical survey of these, along with those previously reported, with pregnancy, focuses attention upon certain prominent features. Sydenstricker,¹ in reporting the first two cases, did not furnish clinical descriptions, so that actually only 21 cases can be reviewed. All but three of the patients were less than 30 years of age, the oldest was 35 and the youngest 16 years. Six died as a complication of pregnancy. Thrombotic phenomena were suggested by the clinical course of ten, seven of these had signs and symptoms of pulmonary infarction, two of cerebral thrombosis, three of thrombi in the legs or vessels of pelvic and abdominal viscera. Nine gave histories of spontaneous abortions, miscarriages, or both. Thirty-two of the pregnancies were reported as having progressed beyond seven calendar months. Twenty-four of these survived, and eight died either in utero, at delivery, or soon afterward. Nineteen of these infants were examined for sickling, and fourteen reported as positive.

The blood pressure was reported in thirteen cases (including the three reported here): seven had hypertension (diastolic blood pressure over 90 mm. of mercury). In Case 1 of this series, there was albuminuria, declining kidney

PEPTIC ULCER WITH HEMORRHAGE DURING PREGNANCY AND FETAL DEATH

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THE frequency with which epigastric distress, heartburn, and sour belching are complained of in the latter weeks of pregnancy indicates that there exists functional or organic disease of the upper gastrointestinal tract in a large proportion of gestations. Unfortunately, these symptoms are too often taken as a matter of course by the physician. Gravid women who present manifestations of digestive disease or disorder are rarely studied for the purpose of discovering their precise nature and cause. Sandweiss and co-workers¹ point out that patients admitted to obstetric or gynecologic hospital services are not, as a rule, questioned closely about gastrointestinal complaints. Yet, in a review of the literature, these authors collected 13 instances of death due to hemorrhage or perforation of gastroduodenal ulcer occurring immediately or shortly after delivery, adding one case of their own. Their report is in contrast with the opinion quite generally held that pregnancy has a beneficial influence on pre-existing peptic ulcer. However, there is evidence to show that such a concept is only partially true.

Clinical and experimental investigations point to a probable relationship between endocrine activity and gastric secretion. From a clinical point of view it is to be noted that 80 to 90 per cent of peptic ulcers in adults occur in men; yet, before puberty the incidence is approximately the same in both sexes (Bockus²). The relative infrequency of peptic ulcer in women appears to be even more marked during pregnancy. Sandweiss, Saltzstein, and Farbman³ were able to find only one proved case of chronic peptic ulcer among 70,310 case histories of patients admitted to hospitals during pregnancy. However, it is possible that closer investigation of the nature of gastrointestinal complaints during gestation would reveal that such a lesion occurs more commonly than is ordinarily suspected.

Another observation made by Sandweiss and his associates⁴ was that 46.7 per cent of 30 women with peptic ulcer showed pituitary, thyroid, or gonadal abnormalities. Bockus² states that the female patient with ulcer should be surveyed from the standpoint of endocrine abnormality because of the high incidence of endocrinopathies reported among women having peptic ulcer.

Experimental evidence further supports the theory that an endocrine factor is in some manner concerned in the control of gastric secretion. Sandweiss and his co-workers^{3, 4} injected anterior pituitary-like hormone (chorionic gonadotropin) into laboratory animals following Mann-Williamson operation and noted a reduction of the incidence of jejunal ulcer. Furthermore, these investigators,^{3, 4} as well as other workers,^{5, 6} found that extracts of pregnancy urine or urine extracts from nonpregnant women without ulcer and from men similarly free from peptic ulcer caused a decrease in peptic ulcer in experimental animals. According to Gray⁷ and Friedman and Sandweiss,⁸ larger doses of such ulcer-preventive urine extracts also inhibit gastric secretion to some degree. Culmer, Atkinson, and Ivy⁶ found that the injection of chorionic gonadotropin into dogs with Pavlov pouches greatly diminished the secretion

2. Two of these patients presented signs and symptoms of toxemia of pregnancy.

3. In sickle cell anemia with pregnancy vascular phenomena, particularly thromboses, occur frequently. These phenomena may, in these instances, bear an important relationship to the occurrence of, or the severity of, the symptoms of the toxemia of pregnancy.

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Addendum

A fourth case has been observed since submission of this paper for publication. A 19-year-old Negro primigravida, at term, with sickle cell anemia, delivered spontaneously after eight hours of labor, a 4 pound, 10 ounce male infant (Jan. 21, 1947). The next day she developed signs of bilateral basilar pulmonary atelectasis followed by a nonspecific pneumonitis with slow recovery. The infant's blood did not show sickling. It gained weight slowly, developed diarrhea, and died at the age of two months.

tionable jaundice appeared on one occasion. In 1938, following cholecystectomy, she again experienced a temporary remission of symptoms. The pathologist reported that the gall bladder showed chronic cholecystitis and cholelithiasis. Thereafter, at intervals of three to six months recurrences of epigastric pain were relieved by nonsurgical biliary drainage. Fractional gastric analysis, which was done during the course of this series of biliary drainages, was said to be normal. Radiographic studies were not made. The patient became free from gastrointestinal symptoms about October, 1942, and remained so until the last trimester of the present pregnancy.

As a child the patient had been thin, but became rather obese at puberty, retaining this tendency to the present time. Menstruation began at the age of 13 years, was regularly established from its inception at a 28-day interval, with a normal flow lasting four to five days. She was married in 1944 at the age of 34 years. In 1945, the basal metabolic rate was minus 8 per cent. In April, 1945, the patient aborted spontaneously after six weeks of pregnancy. For this reason she was maintained on oral progestin during the course of the present pregnancy. The family history contains no relevant data.

When seen by me on April 11, 1946, sixty hours after her admission to the hospital, the patient had shown some improvement in that the vomiting had largely, although not completely, subsided, there had been no hematemesis for forty-eight hours, and the pain had abated somewhat. Physical examination revealed an obese, slightly pale, gravid woman with no definite endocrine or other abnormalities. The blood pressure was 120/80. At this time the blood count showed hemoglobin 12 Gm. (81 per cent); erythrocytes, 3,700,000; and leucocytes, 14,900. Urinalysis was negative except for the presence of a trace of albumin.

The patient was placed on a Meulengracht regime, together with phosphalgel, tincture of belladonna, and phenobarbital. During the night of April 12 she suffered a severe gastrointestinal hemorrhage, as evidenced by the rapid appearance of marked pallor, weakness, dyspnea, and apathy. Early on April 13 the blood count revealed hemoglobin 3.5 Gm. (24 per cent); erythrocytes, 2,050,000; and leucocytes, 11,000. Repeated small transfusions of whole blood failed to halt the downward course of the blood count which, on April 16, reached a level of 2.7 Gm. (19 per cent) hemoglobin, 1,550,000 erythrocytes, and 27,000 leucocytes (neutrophils 84 per cent, lymphocytes 9 per cent, monocytes 7 per cent). Surgical intervention to halt the gastrointestinal hemorrhage was considered out of the question. Cesarean section was believed equally hazardous. Later in the day (April 16) neither fetal heart sounds nor movement could be detected. On April 17 it was noted that the patient's digestive complaints had abated very markedly. From that point the manifestations of peptic ulcer continued to improve progressively, and there was good response to transfusions and no further sign of hemorrhage.

A stillborn, somewhat premature male child was born spontaneously on April 19. The mother showed no ill effects from six hours of labor. The puerperium was uneventful.

On May 2, fractional gastric analysis revealed the results shown in Table I.

Radiographic study on May 3 was reported as showing the esophagus and stomach to be normal in all respects. "The pylorus opened immediately. The duodenal cap was readily visualized and was seen to be large and rather flabby in tone. At the base, near the lesser curvature side of the cap, was a persistent small filling defect with a small fleck of barium in its center. The stomach was completely empty within three hours after the ingestion of the opaque meal."

of free and total hydrochloric acid, even after histamine. They were unable to produce such an effect with any other hormone.

Reports by Nakai,⁹ Arzt,¹⁰ Mason,¹¹ and Anderson¹² indicate that early in pregnancy there is a marked diminution of free hydrochloric acid secretion. Arzt and Anderson also pointed out that the lowest secretion of free acid coincides with that period of pregnancy in which nausea and vomiting are common. Strauss and Castle¹³ not only confirmed the presence of diminished gastric secretion in early pregnancy in normal women, but also showed that there is a rise in the secretion of free hydrochloric acid in the last month of pregnancy, and a still greater increase immediately or shortly after delivery. Way¹⁴ has presented evidence to show that in human pregnancy there is an inversely proportional relationship between the free and total acid in the gastric secretion and the amount of chorionic gonadotropin in the urine. The normal peak of chorionic gonadotropin excretion in the urine which occurs within the first trimester of gestation, with a subsequent decline, is too well known to require discussion.

The inhibiting influence of extracts of the posterior lobe of the pituitary gland on gastric secretion was reported by Pol¹⁵ and confirmed by Hess and Gundlach,¹⁶ and Dodds and his co-workers,¹⁷ and Metz.¹⁸ Erosions of the stomach or duodenum following repeated or large injections into experimental animals of preparations of posterior pituitary extract have been found by Nedzel,¹⁹ Dodds and Noble,¹⁷ Berg,²⁰ and Metz.¹⁸ Nedzel considered these lesions to be the result of local ischemia due to intense vasoconstriction.

The following case report emphasizes the necessity for attaching greater importance to gastrointestinal symptoms occurring during the latter months of pregnancy:

K. C., a 35-year-old gravid white woman, was admitted April 8, 1946, to Frankford Hospital on the obstetric service, complaining of heartburn, sour belching, and vomiting blood. She menstruated last on July 27, 1945. The expected date of delivery was May 2, 1946. About March 18, 1946, the patient began to experience epigastric discomfort one to one and one-half hours after taking food or medication. At this time heartburn and sour belching were also noted. However, although only casual mention of them was made on her visit to her physician on March 25, these symptoms increased in intensity so that by April 1 the upper abdominal discomfort had reached such proportions as to cause the patient to eat very little. There had also appeared pain in the back coincident with and at a point opposite the epigastric pain. The patient also began to vomit spontaneously, which afforded her relief from her symptoms. The stools had been black for several months because of ferrous sulfate which had been prescribed because of a mild anemia of pregnancy. Having stopped all medication for one week on her own initiative because of the severe epigastric pain, the patient became alarmed when she saw that the stools continued to be tarry. On April 7 she noted blood in the vomitus and on April 8, during a routine office visit, acquainted her physician with the severity of her complaints for the first time.

The patient's past medical history included mumps and measles in childhood and pleurisy at the age of 28 years. The systemic review was negative except for the gastrointestinal tract. In 1930, as a student nurse, the patient began to experience repeated attacks of acute epigastric pain. In 1931, following appendectomy for this complaint, she was free from discomfort for several months. However, the symptoms reappeared, remaining without interruption for several weeks at a time. The patient could not recall any relationship to food or to any procedure or medication taken for relief of the pain. There was no associated heartburn, sour belching, vomiting, or melena. Ques-

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TABLE I

| TIME | TOTAL ACIDITY | FREE ACIDITY | OCCULT BLOOD |
|---------|---------------|--------------|------------------|
| Fasting | 43 | 23 | very faint trace |
| 15 min. | 30 | 10 | very faint trace |
| 30 min. | 35 | 25 | negative |
| 45 min. | 70 | 28 | negative |
| 1 hour | 80 | 40 | negative |
| 75 min. | 90 | 40 | very faint trace |
| 90 min. | 75 | 30 | positive |

When the patient was discharged on May 24, 1946, her blood count showed hemoglobin 10 Gm. (68 per cent), erythrocytes 4,170,000, and leucocytes 7,300. Her digestive symptoms had almost completely disappeared and, except for very occasional mild epigastric distress, she has remained free from gastrointestinal complaints.

Comment

The impression that pregnancy causes beneficial effects in the course of peptic ulcer has some experimental and clinical basis to support it. However, it appears that such favorable influences can be expected only in the early months of gestation. In the last trimester, and particularly shortly after delivery, endocrine influences may cause ulcer complications of a serious, and even fatal, character. It becomes necessary, therefore, to give more than casual attention to complaints referable to the upper gastrointestinal tract during pregnancy. A history suggestive of previous gastroduodenal ulcer should raise the possibility of reactivation of the lesion during the course of the gestation. Sandweiss¹ has emphasized the fact that most peptic ulcer patients have a "past." As in the present case, the routine administration of iron may mask tarry stools due to gastroduodenal bleeding. More frequent blood counts and even examination of the stool for occult blood, after suitable preparation of the patient, may give important information in women less seriously affected than the case reported.

Failure to observe the indications of possible peptic ulcer may result in serious consequences not only for the mother but for the fetus as well. Sandweiss¹ noted that in the 14 cases of maternal deaths reviewed by him, perforation of or hemorrhage from peptic ulcer occurred immediately or shortly after birth of a premature or a full-term child. In the present case, it seems likely that the profound anemia in the mother resulted in anoxia which was the immediate cause of fetal death. It is probable that the dramatic change in the patient's course, which followed immediately after death of the fetus, occurred as a result of the sudden alteration in endocrine influences.

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occurred. Since the amnion forms during the seventh to the thirteenth day following fertilization,⁷ the split could not have occurred before the seventh day. On the other hand, when the split occurred, the cells of the germ disc were sufficiently undifferentiated to form two equally potential halves. This is only possible before the germ disc shows a single axial arrangement, at which time the primitive streak simultaneously appears. These are first seen in the 13½-day-old embryo.⁸ We can be reasonably sure, therefore, that the split forming normal monoamniotic twins occurred sometime after the seventh and before the thirteenth days. Splitting of the germ disc before the seventh day should reasonably produce diamniotic twins, and after the thirteenth day, monoamniotic Siamese twins and monstrosities.

Two cases are here described, one from the Richardson House of the Boston Lying-in Hospital and the other from the ward service of the latter institution. They are of interest because there was no tangling or knotting of the cords, either together or singly, and as would be expected, both pairs of infants were born alive and survived, despite being monoamniotic. These are the third and fourth cases in American literature of double live-births; the second and third cases of double infant survival and the first two cases without tangling or knotting of the cords.

CASE 1.—The patient was a white, married, gravida i, due Oct. 1, 1945. She was admitted on September 18 because of spontaneous rupture of the membranes, not in labor.

Family History.—There were no twins in the patient's family. The patient's husband was a twin, his mother having borne two sets of twins.

Menarche occurred at the age of 14-15 years, periods occurring every twenty-eight days, lasting five days, with moderate amounts of flow and no pain. Her last menses began Dec. 24, 1944.

Prenatal Course.—May 25, 1945: General physical examination was essentially negative. Pelvic measurements indicated a gynecoid pelvis. The introitus was nulliparous. Inspection of the cervix was unremarkable except for a small amount of white discharge. The uterus was enlarged to the size of a five months' pregnancy. It was thought that the presenting part was not the head.

August 9: The uterus seemed slightly larger than average for the duration of gestation. A head was felt in the fundus and a breech by vaginal examination. External version was done without difficulty, after which a head was felt dipping into the pelvic brim. A fetal heart could be heard below and also above the umbilicus following the version. X-ray examination revealed a gynecoid pelvis with prominent coccyx and a twin pregnancy.

September 5: By rectal examination, a head was felt to be engaged and the cervix nearly taken up.

Laboratory studies were negative throughout. Her blood was Group AB Rh positive.

Labor.—Early in the morning on September 18, the patient reported that the membranes had ruptured with the painless escape of fluid from the vagina. She was admitted to the Richardson House at 4:45 A.M. with definite evidence of ruptured membranes, not in labor. The cervix was taken up and 2½ fingerbreadths dilated by rectal examination. She was given seconal and demerol sedation. At 7:25 A.M. active labor was in progress with strong, frequent contractions. Additional seconal and scopolamine sedation was given. At 7:45 A.M. the os was almost fully dilated. Full dilation was reached about

MONOAMNIOTIC TWINS

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MONOAMNIOTIC twins are of interest because of their extreme rarity and the high incidence of fetal death associated with this placental anomaly. In 1935, Quigley¹ collected 109 cases from the world's literature, in only 17 of which both infants survived, although in 20 other cases one infant survived. This author added one new case in which one twin survived, this being the first case in American literature that had not ended fatally for both infants.

Since 1935, five more cases have appeared in the English literature; four American, and one British.²⁻⁶ Of these, two resulted in twin live-births,^{4, 5} although one twin of the first set died thirty hours after delivery. In the remaining three sets of twins there was one live baby and one anencephalic monster. (See Table I.)

TABLE I.

| YEAR | AUTHOR | NUMBER OF CASES | DOUBLE LIVE-BIRTHS | SINGLE LIVE-BIRTHS | MONSTROSITIES |
|----------|-----------------------------|--------------------|-----------------------|-----------------------|---------------|
| 1700- | | | | | |
| 1935 | Quigley | 109 | 17 | 20 | 8 |
| 1935 | Rucker | 1 | | 1 | |
| 1935 | Litt and Strauss | 1 | | | 1 |
| 1936 | Frewer | 1 | 1 | | |
| 1940 | Parks and Epstein | 1 | 1 | | |
| 1942 | Jones | 1 | | | |
| 1945 | Coulton, Hertig and Long | 2 | 2 | | |
| Total | | 116 | 21 | 21 | 9 |
| Per cent | | | 18.9 | 18.9 | 7.8 |

According to Quigley, who discusses the possible mechanisms of development of monoamniotic twins, monstrosities occur frequently, eight having been encountered in his series of 109. One is described in the five subsequent cases. The high fetal mortality, however, is due chiefly to tangling and knotting of the cords around each other and around the infants. True knots of the cords occurred in all of the five cases reported since 1935, even in the sets of living twins. Thus knotting of the two cords, usually causing fetal death of one or both infants, seems to be the common accompaniment of twins not separated by a membranous partition.

Recent observation of early embryos by one of us (A. T. H.) allows estimation of the time at which the fertilized ovum must have split to form two normal embryos within a single amnion. This estimation is arrived at as follows: 'The inductive force in the formation of the amnion is the presence of the embryo.' Had the germ disc split before the formation of the amnion, presumably two amnions would then have formed in response to the presence of the two embryos. Therefore, at the time of amnion formation the split had not yet

Prenatal Course.—Early in pregnancy the patient was admitted to another hospital complaining of nausea and vomiting and costovertebral-angle pain. Urological studies revealed slight impairment of renal function, but because of the coexisting pregnancy, it was decided that most of her symptoms were due to hyperemesis gravidarum.

On her first prenatal visit to this hospital the significant findings were a contraction of the pelvic inlet, a uterus enlarged out of all proportion to the dates, and a moderate anemia. A roentgenogram obtained at this time confirmed the diagnosis of twins and of asymmetry of the pelvis.

Urological studies confirmed the presence of moderate hydronephrosis and hydroureter. Gestation was otherwise uncomplicated.

Labor.—The patient was admitted to the hospital as noted five hours after the onset of labor and three hours after rupture of the membranes. The first fetus was presenting by vertex which was well engaged, and the cervix partly dilated. Following a hot enema, labor became satisfactory in effacing and dilating the cervix. After fourteen hours of labor with seconal, scopolamine, apomorphine analgesia, she was delivered by forceps extraction of a 5 pound, 5 ounce female infant in good condition. Spinal anesthesia was employed. Meanwhile the arms of the second fetus had prolapsed into the vagina. These were replaced, and delivery carried out by internal podalic version, breech extraction, with forceps to the aftercoming head. The second infant, also female, weighed 5 pounds, 14 ounces. She did not cry for three minutes, but her color became good after the nasopharynx was aspirated. The placenta separated in six minutes and was delivered by simple expression. The patient withstood the procedure well, having lost an estimated 200 c.c. of blood. The right medio-lateral episiotomy was repaired.

Postpartum Course.—The only complication of the puerperium was cracking of the nipples, necessitating the substitution of formula beginning on the sixth postpartum day. The lesions were treated with penicillin ointment, ice bag, and binder. The mother and both babies were discharged on the sixteenth postpartum day, the first baby having gained one-half ounce and the second having lost three ounces.

Placenta.—The placenta weighed 1,080 Gm. and measured 21 by 21 by 2.5 cm. The cord of the first twin (marked at delivery) was inserted eccentrically and measured 66 cm. in length. No knots or tangles were noted in the cords at any point. The fetal surface of the placenta was homogeneously slate-blue in color with two small white indurated areas suggestive of subchorionic fibrin deposition. No amniotic partition could be discovered. The fetal vessels showed marked interdigitation with actual anastomosis. Membranes were ruptured far from the placental margin. Lobulations upon the maternal surface were normal in depth. There was a moderate degree of calcification in the decidua. The cut surface was purple in color, moist, and granular in texture.

Summary

1. A brief review of the literature on monoamniotic twins is given.
2. An estimation of the time at which the germ disc split to form monoamniotic normal twins is made.
3. Two new cases of monoamniotic twins are described in which both sets of twins lived, this being the second and third instances in American literature of double survival.

11:00 A.M. and, after more than an hour in the second stage of labor without progress, preparations were made for delivery.

Delivery.—Under spinal anesthesia, a head was felt in the midpelvis in left occipitoposterior position. Midforceps rotation and extraction were done with Kielland forceps aided by a median episiotomy. A long version glove was then put on, and the second baby delivered from right occipitoanterior by internal podalic version and breech extraction. The cord was once around the neck. No separate sac of membranes was encountered around the second baby. One ampule of pituitrin was given after the birth of the second baby. A single placenta, complete with membranes and two cords, was expressed after which one ampule of ergotrate was given intravenously.

Infants.—The first baby was a 5 pound, 11 ounce male born at 12:35 P.M. He was slightly cyanotic at first but breathed well. Mucus was removed from the upper respiratory passages and oxygen administered, after which his color was excellent. There were no abnormalities except phimosis.

The second baby was a 4 pound, 11 ounce male born at 12:44 P.M. He was moderately white at first but rapidly became pink, breathing and crying well. There were no abnormalities except phimosis.

Both babies were taken to the premature nursery and given continuous oxygen therapy.

Postpartum Course.—The patient's postpartum course was uneventful except for uterine subinvolution corrected by additional ergotrate and daily hot douches. She was unable to nurse, having insufficient milk. She was discharged on September 30, her twelfth postpartum day, taking the first baby with her. His discharge weight was 5 pounds, 6½ ounces, and his condition good.

The second baby was discharged in good condition on Oct. 7, nineteen days after delivery, weighing 5 pounds, 6 ounces.

Placenta.—*Gross:* The placenta weighed 820 Gm., and measured 26 by 27 by 2 cm. The membranes were ruptured from the placental margin. There was only one amniotic cavity, no membranous partition being present between the two umbilical cords. One cord was attached 4 cm. from the placental margin, and measured 41 cm. in length; the other cord also arose 4 cm. from the placental margin, 8 cm. from the first, and measured 39 cm. in length. The cords were not tangled or knotted at any point. The fetal vessels from the two cords anastomosed at several points over the fetal surface. The maternal and cut surfaces were unremarkable.

Microscopic: Two slides revealed the villi to be of the mature type. Subsynetial fibrinoid degeneration and calcification were present in moderate amounts. The villous vessels were slightly dilated. There was physiologic intimal thickening of the chorionic vessels. The decidua was unremarkable.

CASE 2.—The patient was a 21-year-old Negro, married, gravida i, due March 8, 1946. She was admitted to the hospital on March 7, 1946, in desultory labor because of spontaneous rupture of membranes.

There were twins in the patient's family, two sets having occurred in the previous generation.

Past History.—As a result of a fall at the age of three the patient had scoliosis, for which she underwent a bone fusion operation in 1938. Her only other serious illnesses were pneumonia in 1937 and several bouts of pyelonephritis treated at another local hospital, most recently in 1944.

Menarche occurred at the age of 13 years. Periods have always been irregular, occurring every twenty-one to thirty-five days, lasting four days. Her last menses began June 1, 1945.

THE SIGNIFICANCE OF DECIDUAL POLYPS IN OTHERWISE NORMAL PREGNANCIES

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ONE of the occasionally perplexing problems confronting the obstetrician and gynecologist is the management of abortions. The decision as to whether a threatened abortion has become inevitable is sometimes difficult to make. The passage of tissues from the uterus is commonly assumed to mean that continuation of the pregnancy is no longer possible,¹ and often this is a signal to empty the uterus by curettage.

It is the purpose of this paper to report three cases which emphasize the importance of determining the nature of any tissue passed. That the expulsion of tissue does not always signify inevitable loss of the pregnancy is revealed in the following case reports. In a little over one year three patients were seen during early pregnancy, all threatening to abort as indicated by uterine bleeding and the passage of tissue. However, the tissue proved to be decidua, and all three pregnancies progressed to term with delivery of normal infants.

Investigation of the literature, including popular textbooks on obstetrics, fails to reveal any reference to such a course of events in early pregnancy, although there is described² a diffuse decidual hyperplasia, noninfectious in origin, which may lead to late antepartum bleeding, and thus be confused with placenta previa.

Case Reports

CASE 1.—O. T., No. 545059, para O, gravida i, first seen on April 3, 1944. The patient stated that her last menstrual period had occurred Jan. 11, 1944. Early in February there had been slight vaginal bleeding. There were no associated cramps or pain. Examination showed the usual changes, of early pregnancy, with no palpable adnexal pathology suggestive of an ectopic. However, there were two small cervical polyps which did not bleed on sponging, and, in addition, a small bit of white material in the external cervical os which proved to be the lower end of a strip of tissue two inches in length and one-eighth of an inch in diameter, resembling a fetal umbilical cord. A diagnosis of probable incomplete abortion was made, and the patient was admitted for observation and possible curettage. Microscopic examination of the strip of tissue showed it to be decidua with some necrosis and purulent inflammation. The Aschheim-Zondek test gave a normal positive reaction. In the light of these findings curettage did not seem justified, and, after three days, the patient was discharged from the hospital. The remainder of her pregnancy was uneventful and culminated in delivery of a 6 pound, 10 ounce normal female infant, after a nineteen-hour labor. The third stage of labor was normal and the placenta revealed no pathology.

CASE 2.—I. Mc., No. 445063, para i, gravida ii, first seen on Aug. 17, 1944, the last menstrual period having occurred on May 4, 1944. On July 17, after driving a tractor for two hours, she noted a bloody brown discharge associated with mild suprapubic soreness, but no other symptoms. The discharge continued daily—more profuse with activity—for one month, when she first sought medical

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As an aid in ruling out the diagnosis of abortion in these cases, use was made of the Aschheim-Zondek test. This test was positive in all three instances. In incomplete or complete abortion one would be more likely to obtain a negative, or incompletely positive reaction.

The practical significance, therefore, of these cases is that the true nature of any tissue passed by a patient threatening to abort must be determined by microscopic study. If fetal elements are included, then one must assume that the abortion is inevitable. If only decidua is found, ectopic pregnancy must be considered. If this can be ruled out, then one is probably dealing with an otherwise normal pregnancy which will require no special care. A positive pregnancy test further confirms this assumption.

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attention. Upon examination the uterus was found to be compatible with a $3\frac{1}{2}$ -to 4-month pregnancy (perhaps a little larger than the menstrual history would indicate, thus suggesting the possibility of a mole). The adnexa were negative to palpation. The cervix was dilated 1 cm. by a polypoid mass of tissue which bled briskly upon sponging. This tissue was removed with a biopsy forceps. Microscopic study showed that the entire specimen consisted of decidua. There were inflammatory infiltrations upon the surface. During the second trimester there were frequent episodes of slight bleeding and cramping, but the last trimester was uncomplicated. The patient delivered an 8 pound, 7 ounce infant at term after a sixteen-hour labor. The third stage was normal. The placenta revealed a succenturiate lobe, but no other abnormality.

CASE 3.—M. T., No. 571771, para O, gravida i, first seen on June 22, 1945. Her last menstrual period had occurred on May 29, but was five days late. After five days (her usual duration) the flow stopped, but two days later it recurred and was profuse. She also had marked nausea at this time. The bleeding ceased following the taking of some tablets, given by another physician. However, it recurred intermittently until she was first examined by me on June 22, 1945. Examination revealed the uterus to be soft and slightly enlarged, and there were a few small bits of necrotic appearing tissue in the external os. These were removed and proved to be decidua, largely necrotic, and with leucocytic infiltrations. No chorionic villi were found. The Aschheim-Zondek test was positive in 1:50 dilution, but a few days later gave only a normal positive reaction. For the next month the patient continued having daily a slight brown or pink discharge. Thereafter, the pregnancy progressed normally, and a 5 pound, $15\frac{2}{3}$ ounce male infant was born at term after a one hour and forty minute labor. The third stage and placenta were normal.

Discussion

It is interesting to speculate as to the origin of the decidual tissue passed by these patients. Possible explanations are:

1. The development of the decida may have been unusually exuberant resulting in a condition similar to the diffuse decidual hyperplasia of earlier writers,² with protrusion of some of the tissue through the cervical canal.

2. Ectopic decidua may be found in the cervical canal (where it rarely occurs, according to Taussig³) with extrusion of a portion of it. In view of the absence of bleeding in the latter part of pregnancy the first theory would seem untenable, for such bleeding is characteristic of diffuse decidual hyperplasia. Furthermore, Stander⁴ has suggested that such a pathologic decidua may interfere with placental separation, which was not encountered in these patients.

The second possibility—ectopic decidua—appears more plausible. No interference with the course of pregnancy or labor would be expected in such a condition.

The passage of decidua in early pregnancy is frequently assumed to indicate the presence of an ectopic pregnancy. That this was not the case in the three patients cited was borne out by the absence of palpable adnexal pathology, and by their subsequent course. This point is of considerable interest and importance, because not infrequently the differentiation between a threatened abortion and an ectopic pregnancy must be made. Passage of decidua would appear to bolster the latter diagnosis (and indeed it often does) but not invariably, as proved by the cases cited here.

At this time a tentative diagnosis of endometrial cyst was made. On April 10, 1946, the patient entered the hospital and an operation was performed for removal of the cyst.

The following pathologic report was recorded:

Gross Examination.—The cyst measured two centimeters in diameter and was removed from the left side of the vulva. The cystic walls were removed in their entirety. A portion of the inner coat was lined with a soft velvety-like mucosa that had a brown yellowish color. Some of this inner coat penetrated the entire thickness of the walls (Fig. 1).



Fig. 2.—Microscopic appearance of endometrial transplantation of episiotomy scar. The well-formed endometrial glands are lined with a single layer of tall cells. The stromal cells are fairly well defined.

Microscopic Examination.—In this tissue there was a great variation of the histologic picture. In some areas there was a decided resemblance of the uterine mucosa, while in other regions this condition did not prevail. The well-formed glands were lined with a single layer of tall cells, and in places the stromal cells were well defined. In other places there was considerable disintegration of the mucosa with discoloration, the result of an old hemorrhage. In some regions there were islands of small poorly formed follicles which were surrounded by numerous stromal cells. Again, there were areas of hemorrhage only. In places this mucosa was invading the other walls of the cyst (Fig. 2).

I wish to thank Dr. M. Holmes of St. Joseph's Hospital, Vancouver, Washington, for photographing and describing the tissue reported in this paper.

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ENDOMETRIAL CYST IN AN EPISIOTOMY SCAR

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ABERRANT endometrial tissue has been found and reported in numerous locations. The chief extrauterine sites in which endometrial development may occur, according to Novak,¹ are the following: (1) ovaries, (2) uterine ligaments, (3) rectovaginal septum, (4) the pelvic peritoneum, covering the uterus, tubes, rectum, sigmoid, and bladder, (5) umbilicus, (6) laparotomy scars, (7) hernial sac, (8) appendix, (9) vagina, (10) vulva, (11) cervix, (12) tubal stumps. There may also be involvement of the brachial region, the thighs, and even the lungs.



Fig. 1.—Endometrial cyst removed from episiotomy scars. Gross tumor measured two centimeters in diameter.

Case Report

Mrs. H. A. S., aged 38 years, housewife; good general health; two children, ages 4 and 2 years. Menstrual cycle regular and normal. When the last child was delivered, an episiotomy was performed. About a year after birth of the last child the patient noticed a nodule or swelling located at the site of the left mediolateral episiotomy scar. This gradually became larger as time advanced, and became greatly distended and painful during menstruation. It exhibited a bluish discoloration at this time. On March 21, 1946, an office examination revealed this growth to be about two and one-half centimeters in diameter and rather soft and cystic in appearance. It was opened, and dark-colored blood and what appeared to be disintegrated mucosa drained.

ligament with its tube and ovary. It had its own lower segment connected with the cervix and vagina below. It was the mass in the pelvic cavity which blocked the passage of the fetus. The abdomen was closed after putting in a cigarette drain.

Aside from the purulent discharge through the drainage wound and a low-grade fever for eight days, the postoperative course was satisfactory, considering the patient's condition before the operation. The abdominal wound finally healed by first intention.

On Oct. 26, 1944, or twenty-four days after the operation, the introduction of the uterine sound through the cervical canal showed a uterine cavity of 8 centimeters. Toward the left side, the sound could reach only as far as 4 cm., showing the depth of the cervical stump of the hysterectomized uterus.

Comments

Obstetric literature including the current textbooks would call the above developmental anomaly as *uterus bicornis unicollis*. I had proposed for it the term *uterus didelphys unicollis*. Textbooks heretofore have assigned the term uterus didelphys to two separate uteri with their corresponding cervixes. To this form of anomaly I proposed the name *uterus didelphys bicollis*.

The term uterus bicornis unicollis should be limited to those cases where the separation of the uteri is at the upper segment, not in the region of the internal os which is the condition of the present case. The first report of a case of uterus bicornis unicollis in the Philippines was made by me in 1938.² It was discovered on laparotomy performed for what was supposed to be unruptured tubal pregnancy. What was found was pregnancy of one horn of a uterus bicornis unicollis. The separation of the two uteri was at the upper segment. This patient had given normal spontaneous births without difficulty to ten full-term babies.

In cases of bicornis unicollis (in its limited application proposed by me) because the separation of the uteri is at the upper segment, as long as both uteri have access to the vaginal canal, no dystocia is expected for when one horn becomes impregnated and rises above the pelvic cavity, it invariably raises its partner with it above the pelvic brim; whereas in cases of uterus didelphys unicollis (the new term proposed) as found in the patient here reported because the separation of the uteri is at the internal os or below it, when one uterus becomes impregnated, in its growth, it does not carry with it its fellow partner above the pelvic brim. On the contrary, the nonpregnant uterus because of its softened lower segment remains below the pelvic brim and because it also undergoes hypertrophy, as found in this case, it constitutes a dangerous obstacle to vaginal delivery of a full-term fetus. So that hysterectomy of the pregnant uterus in this case is more than justified. At the time of the operation, the indication was the prevention of the spread of infection. But, in retrospect, its performance removed the danger of causing an obstacle in the vaginal delivery of subsequent full-term pregnancies in this patient.

Braze³ described a uterus similar to the one here reported. No obstructive labor occurred in his case because both uteri became pregnant at the same time ending in the spontaneous delivery of twins. However, three months after the delivery of the babies severe abdominal symptoms occurred in the patient that obliged Braze to laparotomize. He found one uterus was prolapsed and incarcerated. It is unfortunate that both uteri were extirpated.

Summary and Conclusions

1. Uterus didelphys unicollis is the term that should be applied to that developmental anomaly where there is complete external separation of the

FULL-TERM LABOR AFTER A SUBTOTAL HYSTERECTOMY IN A DOUBLE UTERUS

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THE title above sounds apocryphal, but it is nonetheless literally true. On Oct. 2, 1944, because of impending uterine rupture and exposure to infection, the author performed a Porro cesarean section in a woman who, on Sept. 12, 1946, delivered spontaneously her third full-term baby after one-half hour of second stage labor pains. She and her child were discharged from the hospital on Sept. 21, 1946. The full history of the case is as follows:

A. D., para iii, aged 25 years, was admitted to Philippine General Hospital for labor pains. The baby was full term in left occipitoanterior position with the head engaged. After one-half hour of second stage pains, she delivered spontaneously a healthy infant without analgesia or anesthesia.

Previous Pregnancies.—The first pregnancy was associated with marginal placenta previa ending in spontaneous delivery of a small baby less than 6 pounds after a prolonged labor of three days and with the help of pitocin. This child is now 4 years old.

On Oct. 2, 1944, she was admitted to the Philippine General Hospital in serious condition because of dystocic full-term labor of her second pregnancy. She was under the care of an outside private physician who gave her 1 ampule of pituitrin after she had suffered nine hours of strong labor pains and had not succeeded in making the head engage. On admission to the hospital, her temperature was 37.2° C., pulse 103, respiration 20. The uterine enlargement which took an oblique direction with the fundus toward the epigastrium was divided by a transverse groove situated a little above midway between the umbilicus and symphysis. The upper uterine segment was in tetanic contraction, and the lower segment was markedly bulging and tender. The head was the presenting part and was not engaged. No fetal heart was audible. Vaginal examination showed the cervix to be completely dilated, the membranes ruptured, a prolapsed nonpulsating cord, and a high nonengaged head. Pushing the right and posterior fornices toward the vaginal cavity was a tumor mass the size of a large apple which obstructed the engagement of the head.

The diagnosis of impending, if not actual, uterine rupture was made, and laparotomy under local anesthesia was immediately performed. On opening the peritoneal cavity free blood was encountered, but no complete uterine rupture was found. The lower uterine segment along with the bladder was markedly bulging and thinned out. Since many vaginal examinations outside and inside the hospital had been performed, a Porro cesarean section was thought to be the operation indicated. Accordingly, after extracting a large dead child together with its already separated placenta through a longitudinal incision at the upper segment, a supravaginal hysterectomy was made. The uterus was separated from the left broad ligament in the usual manner. On the right side, however, the uterus was found to have neither tube nor ovary, nor was it connected with the right broad ligament. After putting a cervical drain and peritonizing the cervical stump, an examination of the pelvic cavity for the identification of the obstructing tumor showed another uterus enlarged to the size of two months' pregnancy, and to it was attached the right broad

7 SIMULTANEOUS INTRAUTERINE AND EXTRAUTERINE PREGNANCY

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THE first reported case of simultaneous intrauterine and extrauterine pregnancy was by Duverney¹ in 1708. The diagnosis was made at autopsy, death having occurred as a result of rupture of the pregnant tube in the third month of pregnancy.

In 1940, Mitra² extensively reviewed the literature on the subject. He stated that at that time not more than 304 cases had been recorded in the world literature, including German, French, and Russian. He added two cases of his own, bringing the total to 306. Although Stander³ states that the condition occurs quite frequently and has been investigated by numerous writers, most observers consider the condition quite rare. Studdiford and Speck,⁴ in 1944, reported 368 cases with 12 new instances. If one considers that only about 400 cases have been reported since 1708, it is certainly a rarity. Unquestionably many cases are not recognized and others, though recognized, are not reported but it is far from even an occasional experience for the average obstetrician.

In the large majority of cases the symptoms of extrauterine pregnancy predominate. The coincident intrauterine pregnancy is rarely found before operation. Rupture of extrauterine pregnancy most commonly occurs in the first three months.

The treatment of extrauterine pregnancy is definitely surgical, whether the diagnosis is made before or after rupture. A preoperative diagnosis of coexisting intrauterine pregnancy should not in any manner alter the indications for surgical interference. The surgery should be limited to the treatment of the extrauterine pregnancy, and should be as expeditious as is consistent with safety to the patient. Frequently it is impossible to determine definitely a coexisting uterine pregnancy at the time of operation, as in all cases of extrauterine pregnancy the uterus is somewhat enlarged and softened. The removal of such a uterus is definitely contraindicated.

Our report is that of a 25-year-old primipara having a simultaneous intrauterine and extrauterine pregnancy—operated upon following rupture, the intrauterine pregnancy continuing to term.

This patient entered the Colorado General Hospital on Feb. 5, 1945, with a complaint of pelvic pain for the past month. The pelvic pain occurred quite suddenly and became progressively worse until five days prior to hospital admission. At that time the patient experienced a sudden more severe pain confined to the left lower quadrant. This episode was accompanied by nausea and vomiting. The pain subsided in twenty-four to thirty-six hours. No

uteri down to the level of the internal os but have one common cervix. This anomaly at full term will give rise to obstructive dystocia if one uterus becomes pregnant, for the nonpregnant uterus which also undergoes hypertrophy remains in the pelvic cavity.

2. Uterus bicornis unicollic should be applied to those cases where the external separation of the uteri is at the body or upper segment of the uterus. This anomaly does not give rise to dystocia as long as both uterine cavities communicate with the cervical cavity and vaginal canal. When one cornu becomes impregnated, it invariably lifts with it its fellow partner above the pelvic inlet.

3. There is no necessity of removing both uteri in uterus didelphys unicollic or uterus didelphys bicollis. One should be left in situ to perform its normal function.

The outcome of the case here reported justifies such a policy.

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The negative Friedman test can perhaps be explained on the basis suggested by Buxton.⁵ Pregnant patients who have been receiving estrogenic hormone frequently have a negative Friedman test. The secondary signs of pregnancy were minimal. The tender, hard mass present in the posterior cul-de-sac, temperature elevation, and evidence of pelvic pain of one month's duration thus are explained on a basis other than the development of a pelvic abscess which was our first impression.

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specific medication was taken. On the evening prior to hospital admission another episode of left lower quadrant pain occurred. The only therapy the patient had been receiving was some "endocrine injections" from her local doctor for her menstrual irregularities.

Menstrual periods had been of four to five days' duration and occurred every twenty-six to forty-five days. Patient's last normal menstrual period occurred between Oct. 24 and 28, 1944. During November and December the patient flowed one day at approximately the usual time. No vaginal bleeding had occurred since the last part of December, 1944.

Physical examination on admission revealed a white woman of stated age in only slight distress. Temperature was 99.8° F., pulse 120, and blood pressure 120/74. Physical examination was not remarkable except for tenderness on abdominal examination in both lower quadrants. There was some rebound tenderness, more marked on the left side. Pelvic examination revealed the cervix displaced to the right and softer in consistency than normal. A large tender fixed mass was palpable in the posterior cul-de-sac. The fundus of the uterus was not definitely palpable because of the thickness of the abdominal wall and rigidity.

Laboratory findings revealed hemoglobin 11 Gm., red blood cells 3,380,000, white blood cells 10,000, differential; 87 per cent polymorphonuclears, 11 per cent lymphocytes, 2 per cent endothelial cells. Urinalysis showed 3 plus pus cells, 2 plus acetone. Friedman's pregnancy test was negative. The preoperative diagnosis was pelvic abscess, and the possibility of a ruptured tubal pregnancy was considered. We were inclined to regard the menstrual history as unreliable in view of previous irregularity. On February 9, four days after admission, a posterior colpotomy was first done and old blood, blood clots, and fresh blood were encountered. A vaginal pack was inserted because of the amount of bleeding, and the patient was immediately prepared for a laparotomy. A suprapubic midline incision was made and a ruptured left tubal pregnancy was found. A fetus measuring 81 mm. in length, the left tube and ovary, which grossly contained a corpus luteum, and the products of conception were removed. About 250 c.c. of old and fresh blood were removed by aspiration. On inspection the right ovary also contained a corpus luteum. The uterus was about the size of a 2½ months' pregnancy and soft. A diagnosis of intrauterine pregnancy was made. A Penrose drain was placed through the vagina and 5 Gm. of sulfathiazole and sulfanilamide mixture were left in the pelvis. Postoperatively the patient was placed on 15 mg. of progesterone daily during her hospital stay and 5 mg. daily for fourteen days following her discharge. The Penrose drain was removed on the third postoperative day. The patient's convalescence was uneventful. She was discharged from the hospital on her fourteenth postoperative day.

The intrauterine pregnancy progressed satisfactorily, and a viable female child weighing 8 pounds, ½ ounce, was delivered with low forceps on Aug. 22, 1945. The child was normal except for a talipes equinovarus deformity of the right foot. Immediately post partum the uterus failed to contract satisfactorily and the patient lost approximately 500 c.c. of blood. Because of the blood loss, a whole blood transfusion was given. This case illustrates the importance of doing routine Rh blood grouping for transfusions in an obstetric ward, as this patient was Rh negative and her husband was Rh positive.

present on the anterior aspect of the vaginal vault adjacent to the cervical lesion. The lesions were quite odorous. Palpation disclosed that the lesions were soft and that the posterior vault was partially stenosed by firm cicatricial tissue. Dark-field examination of the lesions were negative. After repeated Wright-stained smears, the typical intracytoplasmic Donovan bodies were demonstrated. The patient received a ten-day course of penicillin, mapharsen, and bismuth for early latent syphilis, and then was started on gradually increased doses of tartar emetic. Daily examination during the course of anti-syphilis therapy revealed no change in the character of the lesions. After two weeks of tartar emetic therapy, the vaginal lesions had practically disappeared, the cervical lesion was 90 per cent healed, and the stenotic condition of the vaginal vault was subsiding.

Tartar emetic therapy must be maintained for a period of several months to prevent recurrence of the disease.

GRANULOMA VENEREUM OF THE CERVIX

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(From the Delta Medical Center)

GRANULOMATOUS lesions of the cervix have been described in the medical literature since 1928. Gardner, in that year, first suggested that such lesions might possibly be related to granuloma inguinale, yet it was not until 1937 that granuloma (inguinale) venereum of the cervix was established as an entity by Greenblatt and Pund when the pathognomonic cell was demonstrated in the cervical lesion.¹ Since that time 65 cases have been reported in the literature. In 1934 McGee reported eight cases of granuloma of the cervix diagnosed by biopsy. In none of these cases were the Donovan bodies demonstrated at the time. In 1939, Pund, Huie, and Gotcher, reviewing the Georgia Medical School files, discovered no cases prior to 1934 and nine cases from 1934 to 1938 from a total of 830 cervical biopsies. Arnell and Potekin reviewed all the cases of granuloma of the cervix at Charity Hospital from 1929 to 1937 and identified Donovan bodies in 17 cases (including four of McGee's cases in which the Donovan bodies were found). From 1937 to 1939, they demonstrated the specific histopathology of granuloma inguinale in 21 cases with granulomatous lesions of the cervix. From 1937 to 1939, as far as could be ascertained, seven additional cases were reported in the literature. In 1939, five instances of granuloma venereum of the cervix were reported by Henthorne.

There is a very definite racial difference in the incidence of the disease, the predilection for Negroes being far in excess of that for white individuals. In the Charity Hospital group, there were four cases in white females and 34 Negro cases. All of McGee's and the Georgia Medical School patients were Negroes.

Below are reports of two cases of granuloma venereum of the cervix which were treated at this center in July and September, 1946:

CASE 1.—A 26-year-old Negro single woman was admitted to the Delta Medical Center with a diagnosis of late latent syphilis. The patient had no gynecologic complaints and had had no pregnancies. Routine pelvic examination disclosed a small, 2 by 3 cm., cherry-red, velvety-soft, easily bleeding, irregularly outlined granulomatous lesion located on the anterior lip of the cervix. The lesion was well defined by a smooth, hypertrophied rolled edge. There were no vaginal lesions. Dark-field examinations were negative. Smears stained with Wright's stain revealed the typical intracytoplasmic Donovan bodies. The patient received tartar emetic twice weekly, under which treatment the cervical lesion healed rapidly. At the six-week check-up, the cervix appeared normal with no remaining evidence of the pre-existing lesion.

CASE 2.—A 20-year-old Negro woman was referred to the Delta Medical Center for treatment of "a luetic lesion of the cervix." The patient knew nothing of the lesion and gave no history of pain, discharge, or bleeding. There was one 18-month-old offspring and no history of other pregnancies. The patient had received 10 injections of an arsenical and three of bismuth for syphilis, three years ago. Vaginal examination revealed a 1 by 4 cm. irregular, dirty, friable, easily bleeding granulomatous lesion extending across the anterior lip of the cervix. Three smaller, separate, and distinct daughter lesions were

X-ray examination was done to determine the placental site, and the placenta was visualized on the posterior uterine wall in the middle and lower third. After 350 c.c. of blood had been given, the patient had a chill and the blood was discontinued (patient, a type O, was given type O blood).

During the transfusion the patient began to have uterine contractions, and at its conclusion she was taken to the delivery room and a vaginal examination done. The cervix was two fingerbreadths dilated and partially effaced, and no placental tissue was palpable through the os. The head was well engaged. About 200 c.c. of clots were found in the vagina, but active bleeding had ceased. Expectant treatment was decided upon, and a few hours later she was delivered spontaneously of a living male infant weighing 4 pounds, 8 ounces. Intravenous ergot was given after the birth of the anterior shoulder and the placenta was expressed without difficulty along with about 200 c.c. of clots. Following the expression there was little bleeding, and the patient was returned to her room in good condition. The placenta showed evidence of low implantation with the point of rupture only 5 cm. from the edge. Pathologic report was as follows:

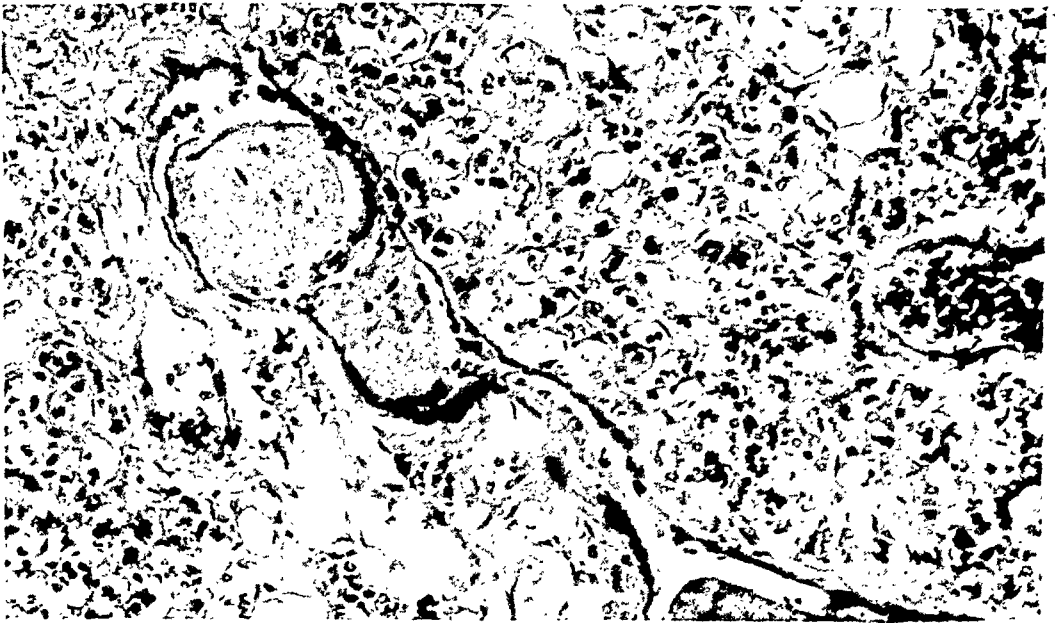


Fig. 1.

Gross: Specimen consisted of a mature placenta and adherent cord measuring about 60 inches in length. The placental membranes appeared to be normal and uniform in consistency. There was a small placenta succenturiate. The fetal surface appeared to be normal. The insertion of the cord was marginal. The maternal surface was made up of well-formed cotyledons. There were no defects in the continuity. The edge of the placenta close to the insertion of the cord showed an area which appeared to be degenerative in character and made up of white fibrous tissue. Adjacent to this was a large sinusoid which was thrombotic.

Microscopic: Several sections of tissue taken from the placenta showed a rather unusual picture characterized by the presence of masses of embryonic capillaries which formed large hemangiomas filled with considerable quantity of blood. Multiple hemorrhages were noted which extended into the supporting stroma. Numerous large sinuses with invading syncytial cells appeared to be somewhat larger than normal, tended to have arborizations, and were unusually

CHORIONANGIOMA OF THE PLACENTA ASSOCIATED WITH LOW IMPLANTATION AND PREMATURE SEPARATION

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CHORIONANGIOMA of the placenta is a benign tumor arising from the chorionic mesenchyme. Whereas the chorionepitheliomas and hydatids arise from the epithelial elements and are relatively common, the chorionangiomas come from the chorionic stroma and are quite rare. The first case was reported in 1798 by John Clarke, and since that time 22 have appeared in the literature. They are known by many names. Virchow called them myxoma fibrosum chorii. Others call them hemangiomas. Beneke (1900) gave them the name of chorionangiomas. Their incidence has been variously estimated from 1 in 7,000 to 1 in 700, but Siddall in the routine study of 600 placentas found six small tumors.

Pathologically, there are three main types; cellular, vascular, and degenerative. Grossly they show considerable variation in size, and may be up to the size of the fetal head. They may be single or multiple, and always have a capsule or a pseudocapsule and are easily enucleated. They are usually on the fetal surface of the placenta, but may be marginal or buried in the placenta. The cellular type is a grayish red, while the vascular type is a deep bluish red. Microscopically they show considerable variation, but most commonly there is a loose groundwork of chorionic stromal cells, predominantly oval in shape, supporting numerous small blood vessels and capillaries. The vessels are usually dilated and filled with blood cells and lined with a single layer of endothelium.

Clinically these tumors are benign, but they may be associated with vaginal bleeding, hydramnios, and premature labor. If the tumors are large they may cause dystocia. In cases of hydramnios and premature labor the fetal mortality may run as high as 30 to 40 per cent.

The present case is reported because of the association of premature placental separation with chorionangioma.

The patient, a 38-year-old gravida vi, para v, was admitted to the hospital with a history of painless vaginal bleeding of seven hours' duration, three weeks prior to term. Her history during her pregnancy was uncomplicated; blood counts and urines were normal, and no toxic signs were present except elevation of blood pressure, which had been 150/86 during the first trimester and 130/78 in the latter months. The total weight gain was 22 pounds. She had had five uncomplicated deliveries in the past 13 years, all the babies being between 5 pounds, 6 ounces and 6 pounds, 6 ounces.

Examination on admission revealed a conscious and well-oriented female who was bleeding vaginally. Her temperature was 98.2° F.; pulse, 84; and respirations, 18. Heart and lungs were normal. Her blood pressure was 118/70. The abdomen was enlarged to the size of an eight-month pregnancy, fetus was in right occipitoanterior position with the fetal heart in the right lower quadrant. Her blood count on admission showed 4,100,000 red blood cells, and 80 per cent hemoglobin which was essentially what it had been during the prenatal course. However, with the history of bleeding a transfusion was deemed advisable, inasmuch as the amount of blood loss could not be accurately determined.

PRIMARY CARCINOMA OF THE FALLOPIAN TUBE

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(From the Beth Israel Hospital)

OF ALL the derivatives of the Müllerian duct, the Fallopian tube is least often affected by carcinoma, while the cervix is the most frequent. According to the literature, the incidence of primary carcinoma of the tube ranges from 0.34 per cent to 1.33 per cent of operations on diseased tubes. At Mount Sinai Hospital, New York, during the years 1928 to 1939, 8,356 patients were admitted to the gynecologic service, and only one case of primary carcinoma of the tube was seen. At Beth Israel Hospital, New York City, during the same eleven-year span, four unquestionable cases of primary carcinoma of the tube were seen.

The preoperative diagnosis of primary carcinoma of the Fallopian tube is very seldom made. Occasionally it has been suspected, and this purely on the sign of intermittent watery and serosanguinous vaginal discharge in women past the menopause. While this clinical feature is suggestive of malignancy of the tube it is by no means pathognomonic. As this condition usually occurs together with other pathology such as uterine fibroids, ovarian cysts, diseased adnexa, etc., it is almost impossible in most cases to single out carcinoma of the tube. However, it is felt that salpingography might be a decided aid in making a preoperative diagnosis of tubal malignancy. It is strongly urged that salpingography be used far more liberally in cases where tubal malignancy is considered. In the two cases to be reported the pathology was such that it is felt that the preoperative diagnosis of carcinoma of the tube might have been made had salpingography been utilized.

Case Reports

CASE 1.—Mrs. M. S., white, aged 53 years, was first seen on April 30, 1945, when she complained of abdominal fullness. She was a para iii, gravida iii, and had no miscarriages. Her youngest child was 24 years old. Her menses began at the age of 13 years occurred every twenty-eight days, and lasted five days. She had had her menopause at the age of 48, five years ago, and no further vaginal bleeding had occurred. Her present illness dated back to 1929, seventeen years ago, when she complained of abdominal fullness. At this time she was told by her local physician she had fibroids of the uterus. She was fairly well for fifteen years until late in 1944 when she again complained of fullness of the abdomen. There was no watery or serosanguineous vaginal discharge present. However, she did complain of malaise and loss of weight. In January, 1945, she again visited her local physician and was told her fibroids grew larger and she needed an operation. On her present admission to the hospital on April 30, 1945, she complained of a loss of 25 pounds in the last six months, and a fullness in the abdomen.

Physical Examination.—Patient looked slightly anemic, otherwise she appeared in good physical condition. Hemoglobin was 70 per cent; red blood corpuscles were 3,800,000; white blood corpuscles, 11,000; and her urine showed a specific gravity of 1020, 2 plus albumin, and no casts. The rest of the examination was negative except for the vaginal findings. The latter revealed an ir-

well vascularized. Many of the villi appeared to contain very little stroma, a layer of Langhan's cells formed the margin. The remainder of the villus was composed of one or more large venous sinuses.

Diagnosis: Chorionangioma of the placenta.

The patient made an uneventful recovery and remained well after leaving the hospital.

Comment

This case is of interest because it presents a combination of a highly vascularized, chorionangiomatous placenta in an abnormally located implantation. The combination of the two conditions undoubtedly was the cause of the premature separation and the premature labor. The slight elevation of systolic pressures acted in this patient's course may have been indicative of a mild toxemia, which would have played a part in the condition, but in the absence of any other signs this is open to question. There were no evidences of hydramnios in this case.

One can postulate that the common occurrence of premature labor in cases of chorionangioma is due to the action of these tumors as foreign bodies in the wall of the uterus, and that in this specific case, due to the abnormal implantation site and the increased vascularity of the placenta, bleeding occurred. Whether or not the changes in the placenta cause abnormalities in its function of producing progesterone and thus further the occurrence of premature labor is a matter for conjecture. I know of no endocrinologic studies in these cases to substantiate or deny this hypothesis.

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regular uterus reaching to three fingerbreadths above the symphysis pubis. To the right of the uterus and contiguous with it was a mass 6 by 6 by 3 cm. which was thought to be a fibroid. The cervix and uterus were freely movable.

Operation.—The patient was operated upon on May 1, 1945, and a myomatous uterus about the size of a 12 weeks' gravidity and a markedly thickened sausage-shaped right Fallopian tube was found. The latter was freely movable, as was the uterus with its fibroids. There were no apparent adhesions or metastasis. A total abdominal hysterectomy and bilateral salpingo-oophorectomy were performed, as the tubal mass was considered malignant, grossly. The patient made an uneventful recovery and was discharged on the twelfth post-operative day.

Pathology.—*Gross:* The uterus was 9.5 cm. long and 5 cm. wide, and contained several almond-sized fibroids. The uterine cavity contained a small polyp 1.2 cm. long. The right tube was elongated. The thin portion of the tube, from tubal angle to the tortuous portion, measured 6.5 cm. The tortuous part was 5 cm. long, 2.5 cm. wide, and 2 cm. thick, and rather solid in consistency. The surface of the thickened area was yellowish with irregular protrusions. On cut section the tortuous portion of the tube was entirely solid and contained homogeneous tumor masses.

Microscopic Examination: Revealed an anaplastic solid papillary carcinoma of the right tube. Mitotic figures were numerous. Carcinoma was not found in the uterus, ovaries, or left tube.

Subsequent course.—The patient felt well for about one year and then complained of abdominal fullness. Examination at this time, April, 1946, disclosed a tender mass 4 by 4 by 3 cm. at the scar of the vaginal vault. Deep x-ray therapy was given.

In the latter part of June, 1946, she was seen again and the mass felt on previous examinations was larger. She complained of some vaginal bleeding. She continued to run a downhill course and died August 1, 1946.

CASE 2.—Mrs. E. L., white, aged 61 years, complained of vaginal bleeding of three years' duration. She was a para i, gravida ii, and had had her menopause fifteen years ago. Seventeen years ago she had an appendectomy, three years ago a dilatation and curettage, and three months ago a cholecystectomy. The previous curettage revealed a secretory endometrium with insufficient tissue for diagnosis. At the time of the cholecystectomy a tumor of the right ovary was noticed. Her present complaint was vaginal bleeding. This was mild in character and intermittent during the past three years.

Physical Examination.—The patient was a rather obese white female whose general examination was essentially negative except for vaginal examination. External genitals were normal. Vaginal outlet was narrow. The uterus was small, freely movable, but pushed to the left by a mass 6 by 8 by 3 cm. The latter was firm, tender, and somewhat fixed. A diagnosis of ovarian malignancy was entertained.

Laboratory Data.—Urine was negative. Her blood count showed 4,000,000 red cells; hemoglobin, 67 per cent; white cells, 8,000. Sedimentation rate was 52 mm. per hour. Wassermann was negative.

Operation.—On July 17, 1945, a total abdominal hysterectomy and bilateral salpingo-oophorectomy were performed under spinal anesthesia. The right adnexus was the site of a tubo-ovarian mass adherent to the cul-de-sac. The left tube was somewhat dilated, while the uterus was essentially normal. Her post-operative course was uneventful, and she was discharged on the seventeenth post-operative day.

Pathology.—*Gross:* A pear-shaped firm right tube was present. No traces of abdominal ostium were present. On long section only its outer layers can be

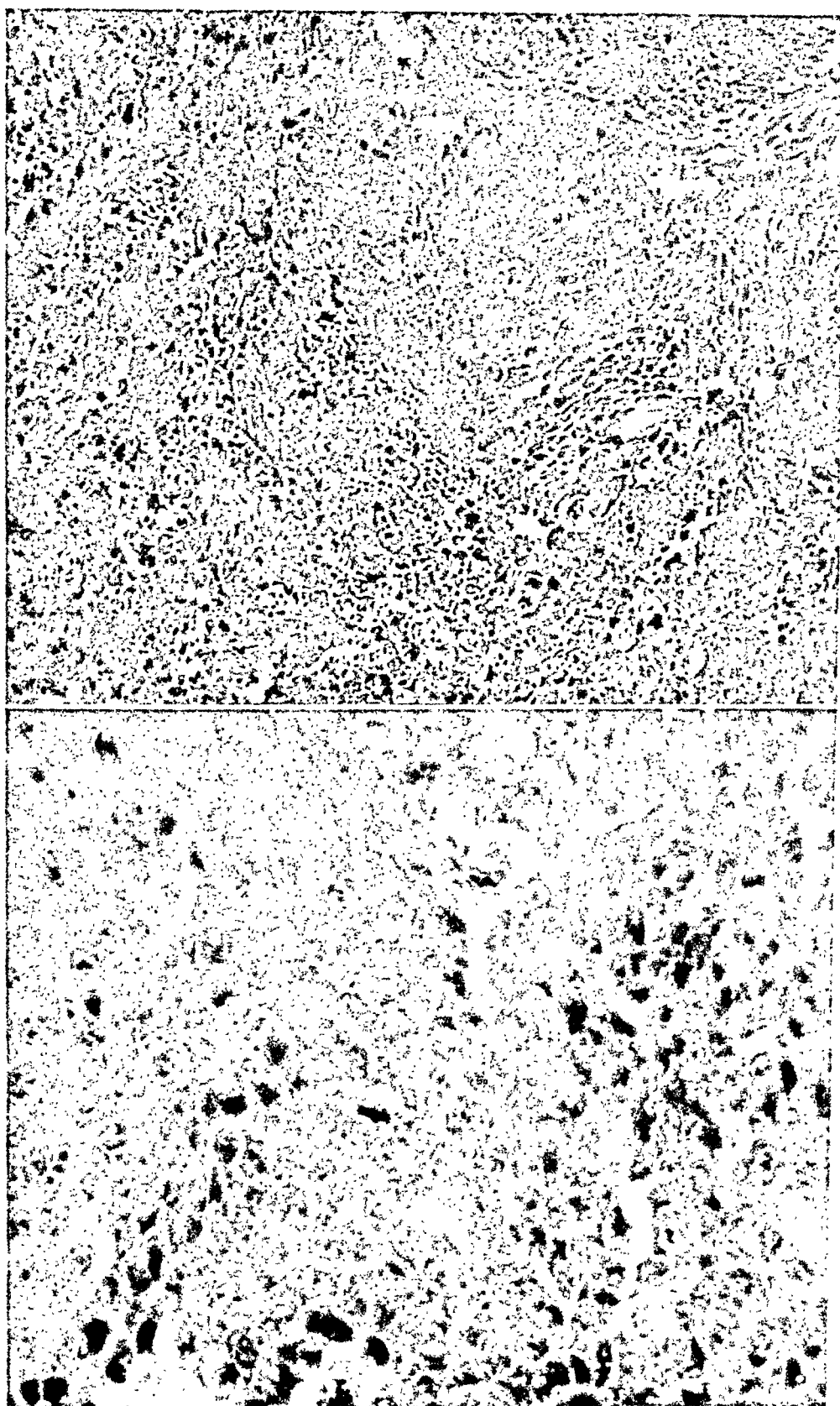


Fig. 1.—Case 1. Cross section of tumor, low power.
Fig. 2. Case 1. Same section, high power.

recognized as tube wall. The remainder consisted of pinkish and yellowish homogenous masses. The other tube was a hydrosalpinx 6.4 cm. by 1 cm. A moderate-sized uterus with nothing remarkable was apparent.

Microscopic: Section through the outer third of the right tube revealed a widely necrotic adenocarcinoma. The other tube was an atrophic hydrosalpinx.

Summary and Conclusion

Two additional cases of primary carcinoma of the Fallopian tube, both unilateral and in the right tube, are herein reported. Neither case was diagnosed before operation. The proper therapy was executed, and yet the first patient, in spite of the completeness of operation and x-ray treatment in addition, succumbed in one year. The second patient is still alive and well, but it is only one year post operative. The literature reveals only an occasional case that survived the five-year cure limit. Neither of these cases gave a history of the symptoms of hydrops tubae profluens.

Hysterosalpingography should be utilized more often in cases of pelvic masses in the postmenopausal age group. In both of these cases, the above procedure might have made the diagnosis preoperatively.

In the first case it was felt that the total abdominal hysterectomy, bilateral salpingo-oophorectomy, and x-ray therapy should have produced a cure, nevertheless she died within a year. The second patient had not received any x-ray therapy and is still alive; however, it is too early to make any definite comments about her survival.

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Addendum

Since this article was submitted, Mrs. E. L. (Case 2), has developed metastases in the pelvis. Biopsy specimen taken from a mass in the vaginal vault revealed carcinoma. She is receiving x-ray treatment, but her condition is poor. This confirms our opinion that these cases do badly, and that the diagnosis must be made still earlier.



Fig. 3.—Case 2. Cross section of tumor, low power.
Fig. 4.—Same section, high power.

Technique

The patient is placed in lithotomy position on the x-ray table. Then a specially devised self-retaining cannula (which itself is an incorporated part of the gynograph) is introduced into the cervical canal. The cannula presents a number of new features including a rotating tip, a revolving acorn, a tenaculum-grasping device and an end-piece which connects directly to the gynograph. After the cannula is secured the patient can assume a more comfortable supine position with legs extended. The gynograph is then placed on the x-ray table between the patient's legs and connected directly to the indwelling cannula.

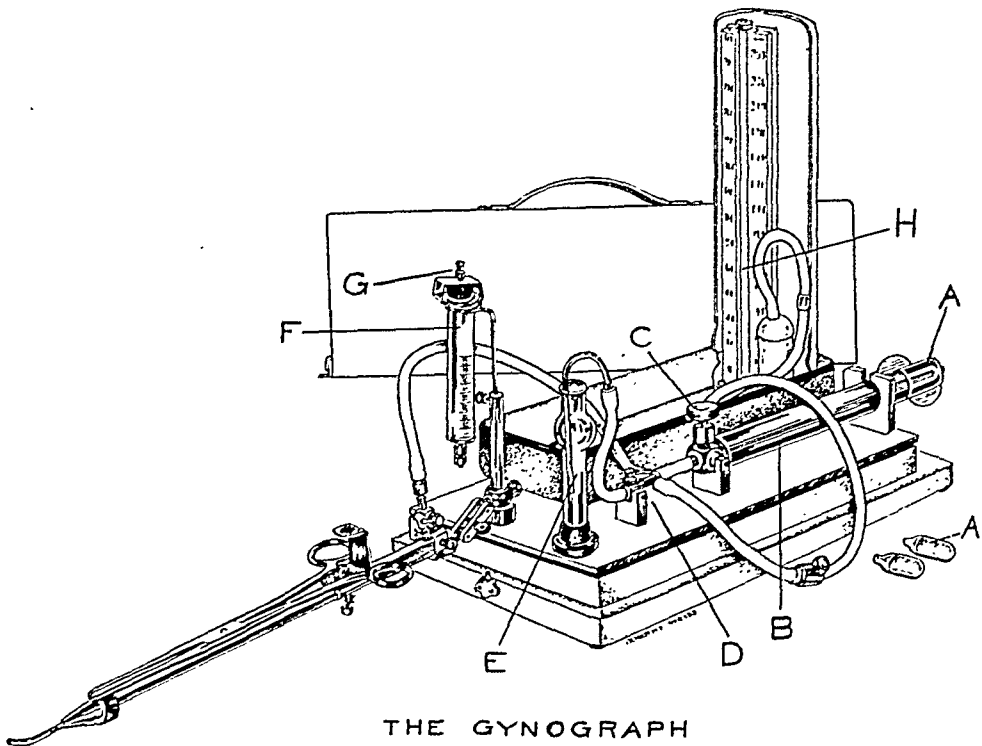


Fig. 1.

The source of carbon dioxide is a very small inexpensive cartridge similar to one used in producing artificial carbonated water. The gas, released from the cartridge (A) by a small piercing device, flows into a cylindrical expansion chamber (B). As the gas expands, the pressure decreases so that it is completely under control of the main valve (C). By a slow counterclockwise turn of this valve the gas escapes. Before allowing the carbon dioxide to enter the patient, the rate of flow is established and predetermined by shunting the gas bubbles (by means of a two-way valve) (D) into an outlet-counting chamber containing water (E). A rate of flow of from 60 to 80 bubbles per minute, or less, is essential for safety. After the rate of flow has been established, the two-way valve is released and the gas is then allowed to flow slowly into the patient through the cannula under manometric observation. From this point on the determination of tubal patency and gaseous entrance into the peritoneal cavity is similar to that of the Rubin test, i.e., with a drop in manometric pressure, tubal patency can be said to exist. The test can be repeated as often as necessary by simply releasing the carbon dioxide into the water chamber and starting over again. If tubal patency is established and a pneumoperitoneum desired, the gas can be allowed to flow into the abdominal cavity for three to five minutes or longer, if necessary, at the same rate of gas flow (60 to 80 bubbles per minute).

A NEW MULTIPURPOSE APPARATUS FOR USE IN THE DIAGNOSIS AND TREATMENT OF STERILITY IN THE FEMALE*†

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IN THE past twenty-five years much progress has been made in the diagnosis and treatment of female sterility. This is especially true with regard to sterility originating in the genital tract. In surveying and evaluating the reproductive tract of the female, three separate and distinct schools of approach have been evolved. Headed respectively by Rubin,¹ Jareho,² and Stein,³ each group advocates a different method of diagnosis. Since 1920 Rubin and the men who adhere to his teaching have used carbon dioxide insufflation almost exclusively. Later, with the development of innocuous radio-opaque substances, Jareho and his followers felt that uterotubal x-ray visualization was the method of choice in evaluating disorders of the female genital tract. Finally, Stein and his somewhat smaller group have reported that the most valuable diagnostic procedure in female sterility is the combined technique of gas insufflation *together with* uterotubal x-rays. Stein instills carbon dioxide as in the ordinary tubal test, then allows large amounts of gas to enter, causing a pneumoperitoneum. Finally, he injects the radio-opaque substance and obtains x-ray visualization. By this combined contrast method most excellent visualization of all the pelvic organs (including the ovaries) can be obtained.

Each of the above-mentioned three procedures is a valuable diagnostic agent and each has its place in gynecology depending upon the individual patient and the presenting problems.

It is not within the province of this short paper to expound the well-known virtues of any particular one of the three procedures. Medical discussions of the "pros" and "cons" of each method will probably go on for decades. The purpose of this paper is simply to introduce a new apparatus, the "Gynograph," so constructed that the physician has the facility to perform with this single mechanism whichever one of the above-mentioned tests he desires. He may also perform all three tests simultaneously. This compact apparatus is believed to be a highly efficient portable instrument for either office, clinic, or hospital work.

After seven years of extensive trials the gynograph was finally evolved. And while its facilities are multiple, its dangers are minimal to the patient. For example, in 1,100 tests performed by the author over the seven-year period, the apparatus has been highly satisfactory clinically. It is interesting to note that, owing to the safety factors of the instrument, not one serious mishap resulted.

The mechanical principle employed in the gynograph consists essentially of a completely closed gaseous circuit which is constantly under manometric control and in which carbon dioxide, under pressure, is the motivating force. Thus, not only can carbon dioxide be insufflated, but in addition the same source of carbon dioxide is used as the *vis a tergo* for the instillation of the radio-opaque oil.

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†With the technical assistance of Mr. John L. Marco of Goodman-Kleiner Co., New York, N. Y.

PAINLESS LABORS FOLLOWING PRESACRAL NEURECTOMY

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THE following report is that of a patient who underwent presacral neurectomy for dysmenorrhea in 1941 and had painless labors associated with uterine inertia in 1942 and 1944. No similar case of such profound uterine inertia and abolition of labor pains has been reported following presacral neurectomy.

Cases of pregnancy following presacral resection indicate that there is no interference with the normal progress of labor. The first stage is generally agreed to be relatively painless, but no difference in the intensity or frequency of pain has been noted in the second stage.¹

Cotte^{2, 3} stated that in more than fifty patients who had had resection of the superior hypogastric plexus no effect was noted in subsequent parturition.

Davis⁴ reported two cases in whom labor was precipitate and relatively painless.

Wetherell⁵ described the case of a patient who became pregnant thirteen months after operation. Labor pains were irregular, weak, and confined to the back. She had no pains in front. The position was right occipitoposterior. The first stage was conducted under morphine and scopolamine and lasted eighteen hours. The second stage lasted five hours and was terminated by Scanzoni rotation and forceps extraction.

Donaldson⁶ observed three patients who became pregnant after operation and states that the "labor pains were the same as in an ordinary patient."

Reed⁷ in two patients found no change in nidation, pregnancy, and parturition, although in one cesarean section was done for kidney failure and a fibroid uterus.

Pearce⁸ cited the case of a 20-year-old girl who was delivered of a 9½-pound baby in 1932 after six days of labor. In 1937 presacral neurectomy was done. In 1938 she delivered an 8½-pound baby in 1½ hours with only three hard pains. He states "that in some patients, probably only a small proportion, the first stage of labor is painless and rapid or else unobserved."

Spackman,⁹ in a series of 100 operations, had records of nine patients who subsequently gave birth to twelve children. Labor was less painful, especially in the first stage; the labor mechanism was not altered.

Hendrick¹⁰ reported two cases each of whom had two normal pregnancies.

Rutherford,¹¹ in a careful analysis of eight cases who had obstetric follow-up, found no disorder of function as a result of the operation. Labor pains were absent during the first stage of labor in five of the eight cases. Pain was absent during the greater portion of the first stage in two other cases. It was found that the duration of labor may be somewhat shortened.

Salgado¹² reported an easy short labor four years after presacral neurectomy.

Case Report

Mrs. A. R., a 25-year-old housewife, was first seen on Feb. 1, 1941. Her menses had begun at 14 years of age, were regular every twenty-eight days, and lasted four to five days. The flow was moderate in amount. She had had

Finally, for uterotubal x-ray visualization an ordinary 10 c.c. syringe containing 5 c.c. of a radio-opaque oil, already set up on a rack (*F*), is swung over and inserted into the cannula. The gas is then directly connected to an adapter attached to the top of the syringe (*G*), completing the circuit once more. Under direct carbon dioxide pressure (up to 200 mm.), the oil is forced through the cannula into the uterus and tubes. As the oil enters, x-ray pictures are fractionally taken in the usual manner. During the entire process of tubal insufflation and hysterosalpingography, the hands of the operator are entirely free for fluoroscopy, etc. (The manometer [*H*] and other parts of the instrument are prepared with a luminous paint for use in the dark room.)

In this paper it is not necessary to go into the details of the preliminaries to tubal testing, such as complete vaginal examination, blood sedimentation rate, premedication, local preparation, etc. These important preliminary steps should be employed here with the same care and precaution as they would be in the ordinary Rubin test or hysterosalpingography.

Summary

A new instrument, the "Gynograph," for use in evaluating the status of the female genital tract in sterility studies, is presented. With this single apparatus, tubal carbon dioxide insufflation, uterotubal x-rays, and pelvic viscerography can be performed easily.

In the author's hands this simple compact portable device has proved highly satisfactory in 1,100 clinical tests.

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spontaneous rupture of the membranes on Feb. 2, 1945, at 3 P.M., and weak painless ineffectual contractions were noted. After twenty-four hours of weak irregular ineffectual cramps, small repeated doses of thymophysin caused moderately strong uterine contractions, and she was delivered at 7 P.M. spontaneously of a 6 pound, 11 ounce boy. Again no pain was experienced until the head distended the perineum. The total duration of labor was twenty-nine hours and twenty-three minutes. The postpartum course was uneventful.

At the present time she feels well and is menstruating regularly every 28 to 30 days for four days. She occasionally has slight lower abdominal discomfort and distention on the day prior to menstruation, but has no actual cramps or pain. Her uterus is slightly enlarged and irregular.

Comment

The actual and theoretical effects of presacral neurectomy upon labor cannot be understood without a knowledge of the innervation of the uterus. Unfortunately, there is considerable confusion both as to the anatomic pathways and physiologic mechanisms involved. "All existing evidence points to the fact that the nerves to and within the uterus are not essential for parturition."¹³⁻¹⁵ However, the fact that labor can take place independently of the extrinsic uterine innervation does not mean that nervous impulses do not influence, at least in part, normal uterine motility and perception of pain. The presacral nerve contains both sensory and motor fibers to the uterus, whereas the cervix, vagina, perineum, and pelvic floor are supplied through independent pathways.¹⁶ The presacral nerve lies above the promontory of the sacrum and is inconstant in morphology. It may vary from a single or double strand to multiple and diffusely separated nerve filaments.^{17, 18}

If this anatomic description is correct, then complete excision of the presacral nerve should theoretically interrupt both sensory and motor impulses to the uterus, and result in painless labor and some degree of uterine inertia, as described in the case reported here. On the other hand, the normal pattern of contractility of the uterine musculature is probably controlled by endocrine factors and distention of the uterus, and is only partially dependent upon the extrinsic nerve supply. That the latter does play some role is best demonstrated by clinical experiments with caudal anesthesia. Peridural block extending to the eleventh thoracic root (where the sensory fibers originate which course through the presacral nerve) abolishes the pain of uterine contractions without abolishing their force.¹⁹ Extending the block to the fourth thoracic segment of the cord or higher (where the motor fibers originate which course through the presacral nerve) significantly impairs the strength of uterine contractions in 69 per cent of patients.²⁰ In fact, caudal anesthesia at this level has been utilized to arrest premature labor to the delay of several weeks.¹⁶

Why alterations in labor to the degree experienced by this patient have not been previously described following presacral neurectomy cannot be answered. Furthermore, since this operation does not interrupt the innervation of the cervix and vagina, it is difficult to understand why the pain of cervical distention was abolished.

It is obvious that many factors beside those of innervation, such as size of the child, mechanism of descent, sensibility of the patient, etc., modify the pain and force of uterine contraction. It is possible that in this patient a favorable anatomic disposition of the plexus may have resulted in a more thorough excision than that ordinarily obtained; it may be that she was predisposed toward primary uterine inertia as a result of fibroids, uterine scars, or a hypothetical endocrine factor. The complete absence of pain even at the

premenstrual cramps since the onset of her periods which had become progressively more severe, especially in the past four years. In the past year, the pain was much more intense and began five days after the completion of a period and continued up to the onset of the next period. Medical measures including various forms of endocrine therapy were unsuccessful in relieving her pain. She had had an appendectomy elsewhere five years ago. She had never been pregnant.

There was a right, well-healed pararectus scar. There was moderate tenderness throughout the lower abdomen, but no masses or rigidity were felt. Vaginal examination disclosed a marital introitus. The cervix was normal. The uterus was slightly enlarged, irregular, and contained small fibroid nodules. The left ovary measured 3 by 4 cm. in size. On Feb. 25, 1941, at laparotomy, the uterus was found to contain numerous superficial fibroid nodules measuring from a few mm. to 3 cm. in size. The left ovary was cystic. A presacral neurectomy, multiple myomectomies, and resection of the left ovary were performed. The postoperative course was uneventful except for retention of urine for the first two postoperative days.

She became pregnant seven months later and labor began on the expected date of delivery June 25, 1942. At 12:30 P.M. she complained of frequency of urination and fullness in the lower abdomen, and the cervix was found to be two fingerbreadths dilated with a slight bloody show, although there had been no back or lower abdominal pain. The fetus was engaged in the right occipitoanterior position, and was smaller than usual. Uterine contractions were weak, painless, transient, and ineffectual, despite the administration of castor oil, a hot enema, and three doses of quinine sulfate (grains V). The following morning, at 5:30 A.M., there had been no progress and 2 minims of thymophysin were given. It was felt that the uterine scars were small and superficial and that there was little danger of uterine rupture.

Uterine contractions occurred every five minutes and lasted thirty seconds and were painless. At 7:30 A.M. the contractions were again weak and irregular, and 3 more minims of the thymophysin were given causing moderate augmentation of contractions for the next hour. At 1:00 P.M., the cervix was three fingerbreadths dilated and uterine contractions were again weak and ineffectual. Pantopon grain $\frac{1}{3}$ and scopolamine grain $\frac{1}{500}$ were given in an attempt to hasten cervical dilatation and not because of any discomfort felt by the patient. Two hours later 2 minims of thymophysin were given and contractions occurred every three minutes and lasted thirty seconds. At 3:12 P.M. the membranes ruptured spontaneously.

At 3:30 P.M., she was fully dilated and, following the administration of an additional 3 minims of thymophysin hard contractions occurred every two minutes and lasted for sixty seconds until delivery. She was encouraged to bear down with each contraction since she did not have any spontaneous impulse to do so.

During the entire labor she had not experienced any pain even when the uterus underwent frequent firm contractions following the administration of thymophysin. At 4 P.M., the head crowned the perineum and she complained of pain for the first time during the entire first and second stages of labor. At 4:10 P.M., she was given gas, oxygen, and ether anesthesia. An episiotomy was performed and a female child weighing 5 pounds was born spontaneously at 4:13 P.M. The placenta was expelled at 4:30 P.M. The total duration of labor was twenty-eight hours and thirty minutes. The postpartum course was uneventful and she was discharged nine days after delivery.

Her second delivery was on Feb. 3, 1945, and was in all respects similar to the first already described, except that the onset of labor was initiated by the

Department of Book Reviews

CONDUCTED BY ROBERT T. FRANK, M.D., NEW YORK

Review of New Books

Gynecology

I. C. Rubin's *Uterotubal Insufflation*¹ is a comprehensive report of his diligent and productive activities in connection with sterility problems during more than twenty-five years.

Part I comprises a discussion of the gross and microscopic anatomy, the pathology, and the physiology of the Fallopian tube. Attention is directed to the fact that the length of the tube as determined by salpingography is considerably greater than is apparent during pelvic laparotomy or after extirpation, the difference being as much as 7 cm. or more, attributable to the stretching force of the injected opaque medium and to intrinsic peristalsis. Other anatomic points receiving proper emphasis are (1) that while the diameter of the tube lumen throughout its outer four-fifths readily admits the passage of a uterine sound, only the finest filiform bougie can with difficulty be threaded through the isthmie and intramural segments; (2) that while the relatively few longitudinal folds of the mucous membrane create a simple histologic pattern throughout the narrower segment of the lumen, they multiply distally to such an extent as to produce a strikingly beautiful and complicated labyrinthian arrangement; (3) the existence of both ciliated nonsecretory and nonciliated secretory epithelium, the former greatly predominating throughout the fimbriated segment and both undergoing cyclic variations; (4) that the muscular layer of the tube wall is considerably thicker in the isthmie segment so that it imparts to the palpating finger the sensation of a solid cord easily mistaken for pathologic infiltration; and (5) the existence of a narrow zone corresponding to the intramural segment which is capable of alternate contraction and dilatation like a true sphincter. Exhaustive roentgenologic studies of normal tubes in living human and animal subjects enabled the author to correct false conclusions drawn from similar studies on extirpated specimens that had undergone rigor mortis. These are considered in detail.

The chapter on pathology of the tubes discusses adequately the congenital and acquired causes of occlusion. Statistical studies, including the author's large experience, on the site of tubal occlusions with reference to the two ends of the tubes, vary considerably. In general, impaired tubal physiology resulting from puerperal infections is more easily restored to normal than when due to gonorrhea, since the latter often results in hydrosalpinx with permanent loss of both the ciliated epithelium and peristalsis. The author adopts a hopeful attitude toward greater success in plastic resections of occlusions at the uterine end with reimplantations through improvements in technique fortified by judicious physio- and chemotherapy, together with tubal insufflation.

In his chapter on physiology of the Fallopian tubes, he reveals the thoroughness and diligence with which he has pursued his investigations in an exhaustive objective and scientific study of this problem. With commendable ingenuity he has utilized uterotubal insufflation, hysterosalpingography with viscorayopaque, hippuran, lipiodal, etc., as well as kymographic records both in animal experiments and on human subjects. By such studies he has convincingly demonstrated tubal peristalsis and antiperistalsis, the exist-

¹*Uterotubal Insufflation*. By I. C. Rubin, M.D., Clinical Professor of Gynecology, College of Physicians and Surgeons, Columbia University. With 159 illustrations, including 4 in color. 453 pages. The C. V. Mosby Company, St. Louis, 1947.

height of a thymophysin-induced uterine contraction during both first and second stages would seem to indicate that the operation played a significant role in the production of the painless labor and the associated uterine inertia.

Summary

1. A case in which two painless labors associated with primary uterine inertia occurred following presacral neurectomy is described. Pain was experienced only when the perineum was distended by the crowning head. No similar case of such profound uterine inertia and abolition of labor pains has been reported following resection of the superior hypogastric plexus.

2. Interruption of the innervation of the uterus by presacral resection may abolish the pain and force of uterine contractions in some patients, although it is well known that the extrinsic nerves are not essential for parturition.

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An interesting chapter is devoted to a discussion of tubal occlusion of nonvenereal origin, e.g., appendicitis, induced abortion, and ectopic pregnancy, with the incidence of pregnancy following insufflation as a therapeutic measure in this group.

Part III is devoted to a detailed discussion of the therapeutic application of insufflation both in primary and secondary sterility and its relationship to other sterility factors. The use of the kymograph in these studies the author regards as indispensable, and the value of insufflation during operations on the uterus and tubes designed to correct pathological occlusions is stressed. In the author's series he reports that of 517 women who became pregnant after insufflation, 419 had 490 full-term babies, and he tabulates 1,037 pregnancies that have followed insufflation in the hands of 65 other workers in this field.

Part IV comprises Chapters 12 and 13, in which are presented a detailed comparison of the diagnostic and therapeutic aspects of insufflation and lipiodol injection, as well as the incidence of complications and sequelae following both methods. Collective reports on 9,821 lipiodol injections showed 17 infections, while in approximately 10,000 insufflations reported by 14 different authors, no complications occurred. The author concludes that since both tubal obstruction and the two important points at which it occurs can be determined by single or repeated insufflation, "it is not necessary to resort to uterosalpingography in order to prognosticate the chances of success of a contemplated corrective operative procedure on the tubes."

Part V includes an historical review of the early use of solutions to determine tubal patency, the modifications of the author's apparatus that gradually evolved from the first model, and of the various gases that have been employed. A brief section is devoted to the treatment of dysmenorrhea by insufflation and another to the application of pneumoperitoneum to gynecology. There is also a complete tabulation of data obtained from a questionnaire circulated among colleagues on two occasions by the author. More than 3,000 of these were distributed, and 356 replies that could be used were received. In Table XXXIV are grouped the replies containing the most complete data. Here the total number of cases insufflated was 41,094. Patent tubes were found in 58 per cent, non-patent tubes in 30 per cent, partially patent tubes in 7 per cent, and spasm in 5 per cent. In this group 7,407, or 18 per cent, became pregnant, 746 occurred within one month, and 809 within two months. In the same group seven embolisms occurred, of which six recovered and one died. All of these were due to the use of air or oxygen. There were no other deaths from insufflation when carbon dioxide was used. Next, the author's demonstration model for uterotubal insufflation is pictured and described. And, finally, there is a brief discussion of application of uterotubal insufflation to bovine and breeding mare sterility.

Certainly no one is as well fitted to write a book on uterotubal insufflation as is I. C. Rubin, and he has done a good job. The method is his own brain-child and his book reveals the immense amount of diligent effort, ingenious research, and clinical application he has contributed to its full fruition over the past quarter of a century. It is safe to assert that during this period no more valuable contribution has been made by anyone to the solution of sterility problems. The book contains a wealth of interesting and illuminating detail, the style is clear and concise, the illustrations are reasonably good, and there is appended a long list of references, and an adequate index. The author is to be congratulated upon the thoroughness and uniform excellence of his sterility work, and his book deserves a place in the library of every doctor who is engaged in the solution of sterility problems.

EDWARD H. RICHARDSON.

In *Progress in Gynecology*, Meigs and Sturgis² have edited seventy articles dealing with practically all phases of this specialty. The distinguished list of contributors was

²*Progress in Gynecology*. Edited by Joe V. Meigs, M.D., Clinical Professor of Gynecology, Harvard Medical School; Chief of the Vincent Memorial Hospital, the Gynecological Service of the Massachusetts General Hospital; Surgeon, Pondville Hospital; Gynecologist, Palmer Memorial Hospital, and Somers H. Sturgis, M.D., Chief, The Vincent Memorial Hospital Laboratory; Assistant Surgeon, Massachusetts General Hospital, 533 pages, illustrated. Grune & Stratton, New York, 1946.

ence of an uterotubal sphincter and its influence on pressures, as well as a number of other interesting phenomena. He found the force of uterine contractions in the nonpregnant state to average between 0.3 and 0.5 mm. Hg to 1.5 mm. Hg as compared with a range of 30 to 40 mm. Hg exhibited by the tubes.

Chapter IV is devoted to a study of the relation of ovarian function to the physiology of the Fallopian tubes. While not uniform or constant, there appears to be a moderate relative increase in uterotubal tone during the midinterval. The exact time of ovulation in women has not yet been accurately determined. Diminished uterotubal tonus as well as of the rate and amplitude of tubal contractions is found with hypofunction of the ovaries. The menopause produces a striking loss of tonicity and constant fatigability of the tubal muscle which, however, can be restored by the injection of follicle-stimulating hormones.

Part II comprises five chapters devoted to the technique of tubal insufflation and its diagnostic application. The prime object of the procedure is, of course, determination of tubal patency or nonpatency as a factor in sterility problems. As special indications the author lists:

1. (a) Primary sterility when all other factors can be excluded; (b) sterility attributable to prior gonorrheal pelvic infection but without signs of activity for six months and with no demonstrable infection present; (c) primary sterility with a history of previous peritonitis of appendicular origin; (d) secondary infection attributable to puerperal sepsis; and (e) cases of one-child sterility.

2. To determine the advisability and type of operation designed for the relief of sterility. He points out that operations upon the cervix for sterility, curettage, and myomectomy for sterility should always follow and never precede insufflation.

3. To determine the condition of a residual tube following unilateral salpingectomy.

4. As a therapeutic measure for tubal sterility.

As secondary indications the author recommends insufflation (1) as a guide during operations for tubal sterility to locate accurately the obstruction and determine its successful correction; (2) to determine the results of salpingoplasty; (3) to test the success of tubal sterilization, by the Madlener or Pomeroy technique. He cautions that here slow insufflation with pressures not exceeding 100 mm. Hg should be used; (4) to produce pneumoperitoneum for radiographic diagnosis of pelvic disease; (5) to relieve dysmenorrhea; (6) to determine the necessity for contraception; and (7) to study the physiology, anatomy, and pathology of the tubes.

As contraindications to uterotubal insufflation he emphasizes (1) the presence of inflammation of the genital tract; (2) menstruation; (3) genital bleeding, because of the possibility of gas embolism; (4) pregnancy; and (5) severe constitutional diseases that contraindicate pregnancy.

He considers the optimum time for insufflation to be the week following a regular period, and enumerates sound and convincing reasons in support of this opinion. His apparatus and its use as an office procedure is pictured and described in detail, together with interpretation of the findings and a discussion of shoulder pains, their cause and management.

In normally patent tubes during insufflation, the mercury column undergoes an initial rise of at least 30 to 40 mm. Hg and oftener between 50 and 100 mm. Hg, then drops abruptly 20 to 40 or more points and fluctuating only slightly during the remainder of the test. In a series of 3,200 sterility cases less than 50 per cent had normal patency and function. Much additional statistical data culled from the author's large and varied experience is recorded with interesting and illuminating discussions. Pressure readings in nonpatent tubes and the technique of localization of the site of obstruction are clearly presented; also, an intensive study of obstructions due to peritubal adhesions, tubal strictures and uterotubal spasm, with a record of ingenious animal experiments imitating by mechanical devices these types of occlusion with analysis of the author's statistics in this category, is given.

of antibiotics, anesthesia, an excellent paper on venous thrombosis and pulmonary embolism by Linton, in which he states bilateral interruption of the superficial femoral veins is a justifiable procedure to carry out on patients over 50 years of age subjected to major abdominal or pelvic operations, especially for malignancy. Horrax cogently discusses the neurosurgical methods for palliation of pain due to inoperable pelvic malignancy.

The book is a valuable contribution to gynecologic literature as it offers definite personal opinions on almost every phase of the specialty by men eminently qualified to discuss the research of recent years, the clinical application of the findings; particularly it gives an extended presentation of the cancer problem, its diagnosis, and present-day therapy.

PHILIP F. WILLIAMS.

One of the landmarks in my student studies occurred in 1898 when I first came across Winter's *Gynecological Diagnosis* in which the clinical part was written by Winter; the gynecologic histology, then in its infancy, by Carl Ruge. Since then the number of gynecologic diagnoses have increased and appeared in various languages, but none, in my opinion, have ever approached Winter's interest, vivacity, and general understanding. Neuweiler has added a *Gynecological Diagnosis for Physicians and Students* to the long list of predecessors. It is really the first one appearing in the German language since the onset of the World War. Its interest is mainly clinical, although all of the newer methods of diagnosis are considered. Wisely, he has not attempted to enter into the minutiae of bacteriological and serological methods of diagnostic measures other than to mention them. A great deal of emphasis is placed on visualization of the uterus and tubes, apparently only with lipiodol. Many x-ray pictures are contained in the text. He considers this type of investigation as nonambulatory. In insufflation, he recommends the Sellheim method of injecting air by means of a syringe, the sole control being a manometer, although the Rubin apparatus is both pictured and discussed. I am, therefore, not surprised that he says that from a diagnostic viewpoint, insufflation is often uncertain and that in at least 18 per cent of so-called "closed tubes" conception occurs. To my astonishment, laminaria are still recommended for dilatation preceding curettage. The content of this volume is a carefully planned description of practically all of the conditions met with in gynecology. Various methods of investigation are detailed, including history taking, examinations, instrumentarium, curettage, obtaining of secretions, and the various special investigative methods of which some have already been mentioned. The author then takes up the various areas of the genital tract in succession. The volume is profusely and adequately illustrated. There are some very beautifully colored plates. On the whole, the author has kept in view the needs of the practitioner, although rarer conditions are likewise adequately described. A very detailed and good description of endometriosis is given. Leucorrhea, sterility, and backache are concluding chapters. The volume is very worth while. If there were not already so many "gynecological diagnoses" in the English language the advisability of translation might arise, particularly as the high price of bookmaking in this country precludes the lavish use of colored illustrations.

R. T. FRANK.

The second edition of Novak's *Gynecological and Obstetrical Pathology*⁴ appears after an interval of nine years. The author has the knack of a top rank journalist in

¹*Lehrbuch der Gynäkologischen Diagnostik für Ärzte und Studierende.* von Dr. W. Neuweiler, a.o. Professor für Geburtshilfe und Gynäkologie an der Universität Bern. 474 pages. Hans Huber, Bern. 1940.

⁴*Gynecological and Obstetrical Pathology.* With Clinical and Endocrine Relations. By Emil Novak, A.B., M.D., D.Sc. (Hon. Dublin) F.A.C.S. Associate in Gynecology, The Johns Hopkins Medical School; Gynecologist, Bon Secours and St. Agnes Hospitals, Baltimore; Fellow, American Gynecological Society, American Association of Obstetricians, Gynecologists and Abdominal Surgeons and Southern Surgical Association; Honorary Fellow, Société Française de Gynécologie; The Royal Institute of Medicine, Budapest; Sociedad d'Obstetricia et Ginecologia de Buenos Aires; Central Association of Obstetricians and Gynecologists; Texas State Association of Obstetricians and Gynecologists; Past Chairman, Section of Gynecology and Obstetrics, American Medical Association. Second Edition. With 542 illustrations, 15 in color. 570 pages. W. B. Saunders Company, Philadelphia. 1947.

selected with attention to the particular interest of each one in a definite topic. Consequently, a very personal attitude tinctures most of the papers in this collection. Almost half of the text is devoted to recent endocrine research, the interrelationship of the various glands, diagnostic methods of functional abnormalities, and the therapy of such disorders. The remaining text discusses the sterility problem, infections, benign and malignant growths, technique of gynecic surgery, and pre- and postoperative care.

The first section on growth and physiology brings out the basis of the physiology of normal and abnormal menstruation, the menopause, blood changes, and the Rh factor in gynecology. Markee gives an excellent discussion on the morphological and endocrine basis for menstrual bleeding. Engle concludes that the excretion of gonadotropins is not related to symptoms of the menopause, but that both are controlled by estrogen replacement. Diamond points out the double risk of the gynecologic patient of sensitization to blood factors. In the section on diagnostic methods, Benedict describes and evaluates the more commonly used assays for testing the status of the endocrine glands. Burch and Phelps regard biopsy method as giving most conclusive evidence concerning occurrence of ovulation. Rakoff discusses the importance and technique of vaginal cytology in ovarian function, while Fremont-Smith and Graham feel the vaginal smear in diagnosis of cancer is an accurate, easier, and earlier method than the older techniques.

In the section on functional disorders, Sturgis offers a new classification of the amenorrheas, which Stein properly stresses as a symptom and not a disease. Hamblen gives a fine and practical presentation on excessive uterine bleeding, while Deutsch writes concisely on the important psychiatric component in gynecology.

The interrelationship of endocrine glands is portrayed in seven notable papers. Nathanson, in discussing hormones in relation to tumors, feels that hormones in themselves are not carcinogenic, but that as a result of excessive stimulation or atypical metabolism of the hormones the tissues of a susceptible person may be conditioned to the action of a carcinogenic agent. Davis regards gonadotropin therapy in ovarian failure as offering little to the patient. Reifenstein stresses the necessity of considering the function of the adrenal cortex and the anterior pituitary in all disorders of the ovary.

There is frequent overlapping of discussion in this book, not necessarily of a contradictory character, but rather of a correlation of different aspects of the same basic question, as for instance this presentation by Reifenstein, the discussion by Pratt on masculinization, virilism and hirsutism, and the section by Dokerty on Functioning Ovarian Neoplasms. In the opinion of the reviewer, this adds to the value of the book. Salmon, after a thorough analysis of androgen therapy in gynecology, is tempted to hypothesize the participation of the endogenous androgens in the sex hormone physiology of the human female. He concludes in the end that the *raison d'être* of androgen therapy stems from its clinical effectiveness.

There is ample discussion by able authors of the various phases of sterility, reproductive infections, and benign growths. Malignancy of the various pelvic areas, always a major problem in gynecologic practice, is considered in a series of twelve excellent papers in which the status and technique of radium and x-ray therapy are set forth, as well as the surgery which may be used. Dresser ably discusses supervoltage x-ray treatment. The senior editor contributes an outstanding discussion on the radical surgical approach to carcinoma of the cervix. Morton says his personal feeling is that pelvic lymphadenectomy should be regarded as experimental only, at the present time it has no established place in the treatment of cervical cancer. In contrast, Nathanson feels that iliac lymphadenectomy should be carried out on a large series of cases to evaluate the effect of radiation on metastatic nodes, the incidence of nodal involvement, and its efficacy as a curative procedure.

Eleven articles discuss changes recently proposed in operative technique. Mason describes the technique and results in his total abdominal hysterectomy. The editors have contributed on enterocele and on tubal sterilization. Aldridge describes his operation for stress incontinence in urine. These descriptions and discussions of the operative techniques favored in the different clinics represented are a valuable part of the book. The final section on preoperative and postoperative care is in reality a discussion of chemotherapy, the use

conduct of labor. Mengert cautions against introduction of infection in the last month, and suggests that therapy of trichomonas should be discontinued during this period. Postpartum sterilization is advocated in all patients with proved hypertensive disease.

There is an extended discussion of the abortion problem. An excellent outline of procedure is offered for patients suspected of having placenta previa. Mengert states that 75 per cent of all cases of placenta previa can be treated by rupture of the membranes with or without scalp traction (Willet's forceps) with minimal danger to the mother and less than 20 per cent fetal mortality rate. Organotherapy in obstetrics is an excellent section. The clinical methods of estimating pelvic capacity are emphasized in discussing cephalopelvic disproportion, and Mengert states that the prognosis of the outcome of labor is the function of the accoucheur and not of the radiologist.

In the conduct of labor, Mengert explains clearly the mechanism of separation and expulsion, and stresses noninterference. In the outline for medical induction, the dosage of pituitary extract exceeds that given by other authors. Later, in discussing prolonged labor, extreme caution is recommended in the use of the drug in inertia uteri. An excellent review of methods for relief of pain in labor ends with a section on the deleterious effects of analgesic and anesthetic drugs, a timely warning for the community obstetrician. The incompatibility of cyclopropane and pituitary extract and the possibility of the combination producing shock are noted. In discussing postpartum hemorrhage, the use of a hot intrauterine douche is recommended as a uterine stimulant. The repair of lacerations, especially complete tears, is well described, but it would appear that too many sutures are used, or at least indicated in the illustration, Fig. 46.

The author states clearly the requisites, the indications, and the technique of forceps operations. He regards the originally described application of Kielland forceps as the ideal method of dealing with arrest of labor in occiput transverse or obliquely posterior positions. This technique may be difficult for the family physician for whom the book is intended. The axioms on cesarean should sharpen attention, ante partum, to the possible necessity of this procedure; the section on "Lack of Indication" raises points worthy of scrutiny in a personal or group series. In this connection the author comments later, in discussing the elderly primigravida, that the importance of the child's life must not be exaggerated beyond the bounds of reason. Version and extraction is regarded as not an elective operation. The practical techniques suggested in the sections on postpartum care and care of the newborn and premature are used on the author's service.

The clinical types and newer therapies of puerperal infection are discussed at length. Droplet contamination is stressed. There are excellent chapters on follow-up examinations, miscellaneous complications of the puerperium, sterility, the emotional stresses of pregnancy, laboratory techniques, and the obstetric and gynecologic nursing techniques of the Parkland Hospital, Dallas. The book is cover full of concisely expressed information and clearly stated directions; as a practical guide for the family physician in his frequent obstetrical problems it could hardly be excelled.

PHILIP F. WILLIAMS.

In this book, *The Essentials of Obstetrics and Gynecology*, the authors, Scott and Van Wyck, have recognized the growing integration of the two subjects in research and clinical practice, and present the basic teaching in them given at the University of Toronto. The text is limited to fundamental principles, but covers practically every topic of value in the two subjects.

The discussions on anatomy and physiology have been skillfully handled to open either division, while the physiology of pregnancy, especially the section on metabolism, is complete as well as concise. The authors add a new phrase "control of the patient,"

The Essentials of Obstetrics and Gynecology, by William Albert Scott, B.A., M.B., F.R.C.S. (Can.), F.R.C.O.G. (Eng.), Professor of Obstetrics and Gynecology, University of Toronto, and H. Brookfield Van Wyck, B.A., M.B., F.R.C.S. (Can.), F.R.C.O.G. (Eng.), Assistant Professor of Obstetrics and Gynecology, University of Toronto, 381 pages. With 91 illustrations, 13 in color. Lea & Febiger, Philadelphia. 1946.

presenting facts in a striking fashion, and the courage to oversimplify in the interest of clear teaching. This enables him, for example, to describe the endocrinology of the menstrual cycle and of pregnancy in a mere eight pages of text.

The new edition contains over 100 new illustrations, a number of which are in colors. Particularly the number of gross illustrations has been increased. The very numerous microscopic illustrations are very excellent, and most illustrative of the text. To comment on only one or two subjects in the contents, although he states that only 30 cases of sarcoma of the vulva are reported, this, in my opinion, gives an impression that the condition is very rare. In my own experience, I have encountered several and never have considered them of sufficient importance to burden the literature with them. Again, in describing senile vaginitis, the bleeding not infrequently is due to the rupture of synechiae, either by the trauma of coitus or even coughing. This deserves mention.

The author's very conservative attitude in doubtful lesions of the cervix, particularly in young women, is to be highly commended, because it contrasts so strikingly with the hysterical attitude now current. The book is sufficiently detailed to be of great value to the specialist and the pathologist, and yet so simply and interestingly written that it has a full appeal to the student and the practitioner.

R. T. FRANK.

The second edition of Schauffler's *Pediatric Gynecology*⁵ has appeared after an interval of five years. It has been rewritten in parts and revised up to date. This was particularly necessary, because the introduction not only of sulfonamides but also of penicillin has altered the treatment of gynecologic infections in children just as much as it has in adults. The discussion on masturbation is very excellent. It individualizes, neither overemphasizing the "evil" as did the old school, nor quite as condoning as the more advanced psychoanalyst. Schauffler trusts more in change in environment, attitude, etc., than in coercion or encouragement. Although he describes circumcision in the infantile female, I personally have never had to resort to this operation. The chapter on abdominal malignancies could be improved by a little more method and orderliness. In my own experience true precocious menstruation is more frequent than the author apparently has encountered. In the excellent chapter on urology, prolapse of the ureter through the urethra is not even mentioned. While this is a rare condition, the importance of recognizing it is great because I have seen death following ill-advised amputation of the protruding edematous ureter. There is also a chapter on proctology. Of importance are the chapters on social service as well as the medical legal aspects applied to sex deviations in female children. The social service aspects are in collaboration with Mary L. Eggleston, those on medical legal aspects with Dan H. Northup and Stuart R. Simmel. All in all, this book is very useful indeed, particularly to the gynecologist who only occasionally sees children and adolescents.

R. T. FRANK.

Obstetrics

This book, *Postgraduate Obstetrics*,⁶ by William F. Mengert, is intended for the physician in the average community who does obstetrics in a general practice. The frequency of a condition or complication, and its capacity for casualty, has been the determining factor in the length of its quite personal and fully explanatory discussion.

The diagnostic errors in pregnancy and in its differential diagnosis are emphasized. Prenatal care is regarded as consisting of observation, detection, and control, and it is noted that the best available prenatal care can be completely vitiated without the proper

⁵*Pediatric Gynecology*. By Goodrich C. Schauffler, A.B., M.D., Assistant Clinical Professor of Obstetrics and Gynecology, University of Oregon Medical School; Visiting Gynecological Surgeon and Obstetrician, Multnomah Hospital, Portland, Oregon; Consultant and Teaching Gynecologist-Obstetrician to China Program, UNRRLA. Second Edition. 289 pages. The Year Book Publishers, Inc., Chicago, 1947.

⁶*Postgraduate Obstetrics*. By William F. Mengert, M.D., Professor and Chairman, Department of Obstetrics and Gynecology, Southwestern Medical College, Chairman Obstetrics and Gynecology, Parkland Hospital, Dallas, Texas. 372 pages with 123 illustrations. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York, London, 1947.

This is a very fine study of the physiology of the pregnant and the parturient uterus, and its response to some commonly used agents. There is no doubt but that the clinical application of the method and a correct interpretation of repeated graphs will be of significant value to the obstetrician in atypical labors.

PHILIP F. WILLIAMS.

The Problem of Fertility, edited by Earl T. Engle,⁹ represents the proceedings of the Conference on Fertility, held under the auspices of the National Committee on Maternal Health, in 1946, and presents sixteen papers on the fundamental biological factors concerned in the physiology of reproduction. Ten of these papers recount the application of such basic principles in animal husbandry. The purpose of this recent conference was to reveal the present status of the investigations of reproduction in domestic animals to a large group of clinicians interested especially in the problem of human fertility. While the papers are indeed excellent, the physician interested in human sterility will gain much from the well-edited discussions which followed the reading of each paper.

Of particular note among these proceedings was the evaluation of the fertility of ova produced by use of pituitary gonadotrophins; the methods used in horse breeding to insure ovulation after insemination; and the fertilizability of the equine sperm. Corner presents a fine article on the ovary at the time of ovulation, and the succeeding discussion brought out the presently understood physiology of the granulosa and the theca. The debate following Coles' article on hormonal control of ovulation showed a variance of opinion in the Conference. There is ample consideration, begun by Pommerenke, of the cervix, its mucus, the content of the mucus, and its relationship to infertility in the human being. Four excellent papers brought out recent vital significant facts regarding bovine, human, and rabbit spermatozoa. Artificial insemination was fully discussed both from the standpoint of animal husbandry and the human problem. Simmons' paper on the cervix uteri in infertile matings summarizes a most important phase of the question, and he proposed what he terms "a normal post-coital test."

This presentation of what has been accomplished by animal breeders and the discussion how the advances may be made useful in the human field make the report of the Conference one of significant value in the study of infertility.

PHILIP F. WILLIAMS.

Surgery in Obstetrics by Keller and Ginglinger¹⁰ describes the practices of the Strasbourg Faculty of Medicine. Two introductory chapters deal with conditions met with before conception, particularly malformation of the genital tract. For absence of the vagina, the Baldwin-Mori operation is still discussed and, in fact, is the only operation in the book which is illustrated. The newer skin plastic methods are described. No mention of nonoperative formation of a vagina can be found. Another chapter is devoted to the non-infectious sequelae of labor. In hematocolpo-metro-hematosalpinx, laparotomy is always insisted upon. The surgery for acquired sterility is mentioned, including salpingolysis, implantation of the tube and ovario-uterine implantation. The authors claim that the world literature shows 5 per cent of successes. Ectopic pregnancy is likewise discussed; also the complications encountered in pregnancy and delivery after the uterus has been subjected to various methods of fixation. In the treatment of therapeutic abortion the method of Boero is advocated after the third month. This consists in the injection of 40 per cent formalin into the fetal sac through an intra-abdominal puncture (!). The authors have not yet had an opportunity to test the efficacy of penicillin. All the various difficulties encountered in pregnancy and labor are described with considerable minuteness.

⁹**The Problem of Fertility**, Proceedings of the Conference on Fertility held under the Auspices of the National Committee on Maternal Health. Edited by Earl T. Engle. 250 pages. With illustrations. Princeton University Press, Princeton, New Jersey. 1946.

¹⁰**La Chirurgie en Obstétrique**. By R. Keller, Professeur de Clinique d'Obstétrique et de Gynécologie, et A. Ginglinger, Délégué dans les fonctions d'Agrégé d'Obstétrique et de Gynécologie à la Faculté de Médecine de Strasbourg. Preface du Pr Reeb. 232 pages. Masson et Cie, Paris, VIe, France. 1946.

in a section which gives directions for her care in a quite specific manner. There is a detailed description of home delivery service, a point well taken in these days of crowded maternity hospitals. Early ambulation is favored after labor.

Contraception forms a separate chapter, and while the authors stress the avoidance of pregnancy in many conditions, they are not equally emphatic as to the need for simultaneous sterilization in connection with therapeutic abortion. The use of the Mann forceps, an instrument with a universal joint between the blades and the shank, regarded as advantageous in persistent occiput posterior positions, is described in an excellent discussion of operative obstetrics.

The second phase of this dual presentation, gynecology is equally well handled, especially the relationship of functional disorders, and physical abnormalities of the reproductive system. The illustrations in this section are beautifully done. Pathology is treated regionally. There is an excellent recapitulation in a separate chapter of previous discussions of abnormal uterovaginal bleeding. The authors go lightly in recommending endocrine therapy. Operative procedures are described briefly, but are well illustrated.

This precise and logical manner of offering the fundamentals and modern practice of both subjects leaves little to be desired in such a combined textbook for either student or general practitioner.

PHILIP F. WILLIAMS.

Doctor Murphy offers in *Uterine Contractility in Pregnancy* the methods and results of a study with a Lorand tocograph, and the conclusions which he has deduced. Some 3,200 individual records of uterine contractions form the basis of the studies. The apparatus, which apparently is easily used, records fetal movements as well as contraction of the uterus. In the former response the apparatus may be useful in helping to diagnose death of the fetus. The tocograph measures primarily the hardness of the uterine muscle, and the tracings exhibit both tone of the muscle and contractions. The author notes that uterine contractility has its greatest increase about the thirty-second week of pregnancy, and the time that this phenomenon appears prior to the thirty-second week indicates significant shorter labors. A single tracing, however, is not sufficient basis for prediction of the type of labor to be expected. An increase in the uterine tone is usually observed in primiparas in the sixth month, but usually later in multiparas; the degree of tone, however, is not of significant value in predicting the onset or character of a labor.

Pregnancy contractions have been studied with regard to the effect of pituitary extract and estrogenic substances. In regard to pituitary extract, Murphy feels that a tetanic type of response to the drug occurs when the dose of the drug was large and when uterine tension was high, and concludes from his observations that the amount of pituitary extract for optimum results in the induction of labor or for a stimulating effect in labor should be extremely small, and only sufficient to produce a uterine reaction. He suggests that the optimum dose in labor should be less than one minim. The effect of estrogens on contractility was variable, but no reaction occurs prior to the twenty-ninth week. Morphine appears to influence the intermittent contractions to a greater degree than the tension of the uterus, and would seem to rest the uterus during labor by reducing the frequency of the contractions.

As to inertia uteri, the problem which originated the study, Murphy found that the tocograph will early distinguish the type of inertia present, and is of value in selecting patients suitable for stimulus by oxytocics. Similarly, repeated tracings during a prolonged labor will register the first appearance of secondary inertia.

Uterine Contractility in Pregnancy, A Study of the Contractions of Pregnancy and Labor under Normal and Experimental Conditions. By Douglas P. Murphy, M.D., F.A.C.S., Assistant Professor of Obstetrics and Gynecology and Research Associate in the Gynecological Hospital Institute of Gynecologic Research, University of Pennsylvania. 156 pages. With 61 illustrations. J. B. Lippincott Company, Philadelphia, 1947.

The illustrations in this edition have been increased to 1,108, of which 211 are in color. Many stages of the mechanism and management of labor are illustrated by selected strips from DeLee's motion picture films. Some of the new color plates are beautiful reproductions of obstetric anatomy and pathology. This edition fully maintains the high position of the book as a modern and complete exposition of obstetrics in every particular.

PHILIP F. WILLIAMS.

Obstetrical Practice by Beck¹³ appears in the fourth edition within a period of twelve years. The excellence of the author's presentation of his teaching in this clinical field has made the text a standard in obstetrical literature. Among the major changes in this edition are the sections on implantation and placentation, the application of penicillin to obstetric problems, and there has been added a very full discussion of amnesia, analgesia, and anesthesia.

In the discussion of implantation and placentation, Beck has modified the chapters to accord with the recent observations of Heuser and Streeter on the blastocyst stage, and the views of these authors, and those of Hertig and Rock and Brewer on the lacunar stage, and the method of implantation as shown in the very early embryos which these men have been able to recover from the human uterus.

In the history outline and the outline of physical examination Beck omits obtaining a history of previous transfusions and of Rh factor determination, although the latter is discussed briefly in the text in changes in the maternal organism, the management of pregnancy, and the etiology of abortion. Any discussion of titer determinations and treatment based on them is not given. There is an excellent discussion of penicillin in maternal infection in the prevention of congenital syphilis. Penicillin is not, however, mentioned in the treatment of gonorrhea in the pregnant woman.

In the new and excellent chapter on the relief of pain in labor practically all the recently proposed methods are discussed as to the advantages and disadvantages. Beck states that local anesthesia combined with demerol and scopolamine is the simplest, safest, and the most satisfactory method for the average woman in the hands of the average practitioner. As to continuous caudal anesthesia he states, "The technique is difficult to master, and the margin of safety for the mother is so narrow that the constant supervision by one capable of recognizing and treating the first evidences of an untoward reaction is imperative." The same words of caution are also applied to the use of spinal anesthesia in obstetrics, while the dangers associated with chloroform, ethylene, and cyclopropane are stressed.

One may again recommend the comprehensive diagrams of the mechanisms of labor, and the profuseness of the serial illustrations in the section on operative obstetrics.

PHILIP F. WILLIAMS.

Greenhill's (1946) Year Book of Obstetrics and Gynecology¹⁴ appears as regularly as the first signs of spring. It proves a handy reference source to look up articles and an even more useful guide for quickly envisaging any new developments in these two subjects. The short but pungent editorial notes are impartial, illuminating, and to the point. The liberal use of illustrations adds to the value of this indispensable guide.

R. T. FRANK.

¹³**Obstetrical Practice**, by Alfred C. Beck, M.D., Professor of Obstetrics and Gynecology, Long Island College of Medicine; Obstetrician and Gynecologist-in-Chief, Long Island College Hospital, Brooklyn. Fourth Edition. 921 pages. With 1,008 illustrations. The Williams & Wilkins Company, Baltimore. 1947.

¹⁴**The 1946 Year Book of Obstetrics and Gynecology**. Edited by J. P. Greenhill, B.S., M.D., F.A.C.S., Professor of Gynecology, Cook County Graduate School of Medicine; Chairman, Department of Gynecology, Cook County Hospital; Attending Obstetrician and Gynecologist, Michael Reese Hospital; Associate Staff, Chicago Lying-In Hospital; Author of *Office Gynecology and Obstetrics in General Practice*; Co-author of the *DeLee-Greenhill Principles and Practice of Obstetrics*. 655 pages. The Year Book Publishers, Inc., Chicago. 1947.

In my opinion, the title "Surgery in Obstetrics" is somewhat misleading, as no attempt is made in describing or illustrating the technical surgical procedures.

The book is illustrated by one of the authors, Keller. He has devised a very simple, striking technique of showing all the cavities in deep black and indicating the parietal walls or structures by lighter line drawing. The book is interesting to read, but offers very little new to the American reader.

R. T. FRANK.

Debiasi, who is Director of Obstetrics at the school of Udine, has written on the *Anemia of Pregnancy*¹¹ covering the cases observed in the clinic of Catania and Sassari. He mentions that no recent Italian studies exist, the last one dating to 1903. This is a large 400-page monograph, on rather poor paper, which is a pity because the blood pictures do not show up as well as they might, although they are sufficiently characteristic to be of value. The anemias dealt with are acute posthemorrhagic, chronic hemorrhagic, the hyperchromic, pernicious, pseudopernicious, and macrocytic. From another aspect, there has been a classification into symptomless oligocytemia, the cidropenic, megaloblastic and aplastic varieties. There are a large number of thoroughly studied cases which are described in extenso. The book should prove of value to both gynecologists and hematologists.

R. T. FRANK.

The ninth edition of DeLee's *Principles and Practice of Obstetrics*¹² represents an extensive revision by J. P. Greenhill. Although much new material has been added, this edition, aided by a new double column format, is 100 pages shorter than the previous one.

Among the new chapters is one on "Minor Disturbances of Pregnancy" treating the items which cause most telephone calls and much of the consultation conversations. In another new section the problem and diagnosis of Postmaturity and Missed Labor with death of the fetus are given. Greenhill advocates induction if one is sure of postmaturity or fetal death. Davidsohn wrote the new chapter on Erythroblastosis Fetalis. It is an extended discussion, but does not mention titer determinations in the mother, or prophylactic cesarean or early induction to prevent fetal damage. Directions which may increase fetal salvage are given in a new chapter on Care of the Premature. A section is added on Circumcision, but the presently popular clamp method is omitted.

In addition to these new chapters many changes have been made in other sections. This is notably so in the discussion of anesthesia and pain relief. Greenhill apparently prefers local infiltration where it is possible, often combining it with pentothal sodium intravenously, and he states he has used cyclopropane extensively and satisfactorily. Spinal and caudal anesthetics are not regarded favorably.

Induction of abortion is recommended in pregnant women who have had German measles in the first three months on account of the danger of congenital abnormalities. There is a full consideration of the use of penicillin in various complicating lesions and diseases.

The section on obstetric endocrinology sums up the physiology of the glands, indications for, and dosages of the various hormones which have been found helpful in obstetric practice, as well as a discussion of the various animal tests for pregnancy and chorionepithelioma.

¹¹*Anemie E Gravidanza*. By Prof. Ettore Debiasi, Direttore Inc. della Scuola di Ostetricia di Udine. Con Prefazione del Prof. E. Maurizio, Direttore della Clinica Ostetrica e Ginecologica di Catania. 400 pages. Dr. Francesco Montuoro, Editore, Milano, Venezia. 1946.

¹²*Principles and Practice of Obstetrics*, by Joseph B. DeLee, M.D., Late Professor of Obstetrics and Gynecology, the University of Chicago; Consultant in Obstetrics, the Chicago Lying-in Hospital and Dispensary, and J. P. Greenhill, M.D., Attending Obstetrician and Gynecologist, the Michael Reese Hospital; Professor of Gynecology, Cook County Graduate School of Medicine. Ninth Edition. 500 pages. With 1,168 illustrations, 211 in color. W. B. Saunders Company, Philadelphia and London. 1947.

time intervals in various human racial groups, the author concludes that environmental and nutritional factors may have a bearing. From a biological standpoint, he regards this sterile period as one of gradual maturation of the endocrine glands until the effect of their secretions has finally brought the reproductive tract into full maturity—nubility.

PHILIP F. WILLIAMS.

Di Paola was commissioned by the Sixth Congress of the Argentine Society of Obstetrics and Gynecology to treat the subject of the *Physiology of Adolescence*.¹⁹ This period approximately covers the twelfth to eighteenth year. The morphology including the somatic and sexual changes, the endocrine aspects and finally the methods of study and investigation are described. There are 27 illustrations.

R. T. FRANK.

Eastman's *Expectant Motherhood*²⁰ has gone through fifteen reprintings since the appearance of the first edition. There can be little doubt that thousands of women have benefited by reading the author's "whys and wherefores" on prenatal care and labor, and that busy office hours of many obstetricians have been helped by the efficient and accepted teachings which the book sets forth. In the new second edition is an ample discussion of nutrition and diet, an understanding of which by the patient will do much to help obstetricians control the frequent too rapid gain in weight. Foods have been divided into seven groups with their values and explanations of their necessity and the proper amount. These concise instructions are a valuable addition to the book. Chapters on clothing and preparation for the baby are excellent. The chapter on painless childbirth is a rational exposition of how pain in labor can be relieved and it should do much to reduce the recurring waves of enthusiasm, by lay publicity, for each new type of relief which may be proposed.

There is probably no better book available to recommend to obstetric patients for necessary information in such a simple and practical form.

PHILIP F. WILLIAMS.

This charming and delightful book *Modeling for Motherhood*²¹ is addressed to all pregnant women, for all of them, or nearly all, are worried about their figure and appearance during and after the event. They need advice and guidance not only in the maintenance of proper and adequate diet, but how to develop their muscles for the coming labor. With proper prenatal care, a woman can carry out her most important function in life without ending up as a "bedraggled wreck." After sound directions about choosing doctors, nurses, hospitals, etc., a great deal of attention is accorded to posture, to exercise, to a manner of living, all of which will contribute to make this period of life a happy rather than a mournful one. And the text is written in an amusing fashion and gaily illustrated. It is free from the didactic and academic style of many of the books on "Motherhood" produced by doctors, although the warnings about possible troubles are not omitted. The book might well be in the possession of every prospective mother and also deserves the attention of physicians.

GEO. W. KOSMAK.

¹⁹Tema Oficial Fisiología De La Adolescencia. Relato Del Dr. Guillermo Di Paola. Sexto Congreso Argentino De Obstetricia Y Ginecología, Buenos Aires, 20 Al 26 de Octubre de 1946. 95 pages. Secretaria Del Congreso, Buenos Aires.

²⁰Expectant Motherhood, by Nicholson J. Eastman, M.D., Professor of Obstetrics in Johns Hopkins University; and Obstetrician-in-Chief to the Johns Hopkins Hospital. Second Edition, revised. 193 pages. With 13 illustrations. Little, Brown and Company, Boston. 1947.

²¹Modeling for Motherhood. By Doris Hale Heinz and Katherine Smith Bolt. Illustrated by Doris Hale Heintz, with foreword by Frederic M. Loomis, M.D. John Wiley and Sons, Inc., New York. 1947. Price \$2.

De Moraes' *Propedêutica Obstétrica*¹⁵ appears in its sixth edition since 1924. The author, who is very prolific, has contributed to the obstetric and gynecologic literature since 1915. The present edition has been brought fully up to date and will continue to serve as a good introduction to the study of obstetrics. The topics of modern hormone studies have been brought up to date. There is a very full description of pregnancy tests. I venture to suggest that it would now suffice to mention the Abderhalden pregnancy test merely for its historical interest. The chapter on toxemias of pregnancy deserves special mention because of the thorough discussion. There is innumerable mention of quoted authorities without a single bibliographic reference.

R. T. FRANK.

The *Transactions of the Rioplatá Obstetrical and Gynecological Society* from the year 1946¹⁶ contains a large number of articles on very diversified subjects in both obstetrics and gynecology. To give an idea of its heterogeneous contents, there are articles on dermatological lesions in pregnancy, a number of papers dealing with radiotherapy (in both malignant and nonmalignant conditions); some papers on technical obstetric procedures such as forceps, cesarean section, continuous epidural anesthesia, and related gynecologic subjects such as arterial hypertension. Many gynecologic technical papers are included. From the standpoint of completeness of the literature, the transactions are worth considering.

R. T. FRANK.

Even if belatedly, we welcome (published in 1943) the first book received from Italy since the war. Merlino's monograph on *Abruptio Placentae*,¹⁷ after discussing what is known on the subject in detail, presents 110 cases treated at the University of Naples. The incidence is unduly high, as only 7,218 pregnant women were delivered during this period, 1937 to 1940.

The world's statistics show such a tremendous variation in results—maternal mortality between 94 and 2.9 per cent, fetal mortality between 94 and 2.9 per cent—that worth-while comparisons are out of the question. Of the 110 cases, exactly half delivered spontaneously; 33 were delivered per vaginam; 23 by abdominal section. This large and well-presented material deserves careful study. The many "errata" found in this otherwise faultlessly produced monograph doubtless are due to the disturbed conditions in 1943.

R. T. FRANK.

Dr. Montagu in this small monograph *Adolescent Sterility*¹⁸ discusses the time which elapses between the appearance of the first menstruation and the ability to conceive and carry a fetus to term.

It is evident from this thoroughly documented study that such a definite time interval does exist, both in the human being and the experimental and domestic animals, the lower mammals, the cow, rhesus monkey, and chimpanzee. In the animal group the interval dates from the first oestrus for a period apparently specific for each animal. After studying the different

¹⁵*Propedêutica Obstétrica*. By Arnaldo de Moraes, Professor Catedrático de Clínica Ginecológica da Faculdade Nacional de Medicina da Universidade do Brasil. 6.a Edição. Revista e Atualizada Pelo Autor. Com 512 páginas e 168 gravuras, das quais duas tricromias. Ilustrações adaptadas e originais de L. G. Loureiro. 495 pages. Livraria Francisco Alves, Rio de Janeiro, Brazil. 1946.

¹⁶*VI Jornadas Rioplatenses de Obstetricia y Ginecología*. Actas Y. Trabajos. Montevideo, 21-22 y 23 de Marzo de 1946. Sociedad Ginecológica del Uruguay. 449 pages. Comisión Organizadora. Montevideo. "Resgal" de Hilario Rosillo, Montevideo, Uruguay. 1946.

¹⁷*Il Distacco Intempestivo di Placenta Normalmente Inserita (con 46 figure nel testo)*. Antonio Merlino, Aiuto e Docente di Clinica Ostetrica e Ginecologica nella R. Università di Napoli. Prefazione del Prof. Salvatore Cappellani. 235 pages. Rosenberg & Sellier, Torino, Italy. 1945-XXI.

¹⁸*Adolescent Sterility. A study in the Comparative Physiology of the Infecundity of the Adolescent Organism in Mammals and Man*, by M. F. Ashley Montagu, Associate Professor of Anatomy, Hahnemann Medical College, Visiting Lecturer, Department of Sociology, Harvard University. 141 pages. Charles C Thomas, Springfield, Illinois. 1946.

tried to simplify not complicate the analysis. However, this large, detailed study, based upon ample material will prove of interest to many enthusiastic therapists who treat their patients much more empirically than does the author.

After excluding organic lesions as surely as is possible, he subdivides the groups on a purely clinical basis—young virgins, young women, 40 years to the menopause, postmenopausal. The effect of therapy—estrogens, progesterones, and male sex hormones are used both in diagnosis and therapy.

R. T. FRANK.

Bishop²⁴ has written a short, 124-page monograph in small format, on practical endocrinology for the practitioner, of which 40 pages are an appendix showing the various preparations of "sex hormones," notwithstanding the fact that this book was written to tell the general practitioner "which hormones to use in treatment" and that the author appears to harbor a rather poor opinion as to the knowledge of the general practitioner. The book is clearly and well written. In addition to treatment, it takes up the various syndromes, such as amenorrhea of which one cause is ascribed to pituitary "shock," dysmenorrhea, infertility, and pregnancy. The pregnancy tests are taken up in considerable detail, as well as hormone assays which are at least referred to. For anyone desirous to brush up in complete knowledge, the book might be of service.

R. T. FRANK.

The second edition of Grollman's *Essentials of Endocrinology*²⁵ has appeared after an interval of six years. It has been brought fully up to date. This book contains an immense amount of fundamental information presented in a very readable and understandable fashion. The introduction to each gland, covering the anatomy, embryology, as well as physiology, is very soundly treated. The transition to the clinical facts thus being smoothed out, are understandable and clearly described. The division of the glands according to their location, that is in the cranial cavity, those of the branchiogenic origin, and those in the abdominal cavity, is a bit startling but nevertheless logical.

The hypophysis is very adequately dealt with. The author says that the clinical inadequacy of the anterior hypophyseal extracts must be faced and yet on page 94, he states, "the anterior pituitary extracts are indicated when there is evidence of hypophyseal cachexia," which shows how difficult it is to resist the pressure exerted by clinicians for some treatment of serious conditions. He states unequivocally that the concept of antagonist and synergist is no longer accepted in accounting for gonadotropic action. He likewise doubts greatly that thyrotoxicosis is due to hyperpituitary stimulation. In fact, throughout the book, he is very reserved in accepting exaggerated claims. His stand on Cushing's disease is that pituitary adenomas are rarely the cause. On the other hand, some cases may be actually due to hypothalamic disease. The author's "metabolic craniopathy" seems to be an "ominum gatherum" on a very weak foundation. Whether the purely embryologic basis for describing the thyroid, parathyroid, and thymus under the grouping of "branchiogenic" is justified should remain an open question.

It is hardly necessary in this second edition to take up each organ seriotim because he has done justice throughout and quite impartially. Some rather important conditions are treated in a very cursory fashion as, for instance, the three-fourth page discussion of dysmenorrhea and the coverage of sterility in a page and a half. There is a concluding

²⁴*Gynaecological Endocrinology for the Practitioner.* By P. M. F. Bishop, D.M. (Oxon). Lecturer in Applied Physiology, Guy's Hospital Medical School; Clinical Endocrinologist, Guy's Hospital; Endocrinologist to Chelsea Hospital for Women. 124 pages. Williams and Wilkins Company, Baltimore. 1946.

²⁵*Essentials of Endocrinology.* By Arthur Grollman, Ph.D., M.D., F.A.C.P., Professor of Medicine and Chairman of the Department of Experimental Medicine, the Southwestern Medical College; Attending Physician and Consultant in Endocrinology, the Parkland Hospital, Dallas, Texas. Second Edition, Revised and Enlarged. 644 pages. With 132 illustrations. J. B. Lippincott Co., Philadelphia. 1947.

Endocrinology

"Ovarian Tumors" in two large volumes has appeared as an independent unit (Vol. VII) of Selye's *Encyclopedia of Endocrinology*.²² The concept of one man undertaking such a gigantic task is somewhat disconcerting, but the author has made a brave beginning. The large volume of 427 pages containing 15,000 references on ovarian tumors, alphabetically arranged according to author, but readily referred to by a simple system, contains references from antiquity to recent years. It covers the literature of every country and every language, but in its completeness does not reach the precision of an *Index Medicus*, as I convinced myself by a rather careful perusal of its pages. Moreover, one may well doubt the value of including 27 references to Atlee (1844-1882) or of L. B. Brown on "ovarian dropsy" 33 references (1840-1871); or the two full crowded columns of references to the "common ovarian cyst," some 320 in number, on page 101 of the text.

The second volume (Ovarian Tumors) is an ingeniously arranged loose-leaf cover containing 284 pages of text plus 60 pages of a "List of Periodicals" with 10 index tabs to facilitate ready reference. The closely printed two-column page really doubles the length of the text. In addition, there are 37 full-page plates averaging from 5 to 9 figures on each, many gross, more microscopic, some x-ray photographs, etc., faultlessly reproduced. The majority are from the author's large collection, though many are from other sources to whom due credit is given.

The text has been planned "to serve as a guide to, and a critical summary of, the relevant literature. . . ." The gynecologist and endocrinologist are the audience sought for. Selye presents eight classifications of ovarian tumors from the literature (Goodall, Conill, Schiller, Novak, Ten Teacher's, Miller, Geist, H. C. Taylor, Jr.) and then the one which he uses in his encyclopedia. This latter is in two columns—benign and malignant, and under each "potentially endocrine neoplasms" and "nonendocrine tumors." Of the potentially endocrine, there are no less than 17 categories.

The text is very systematically arranged, covering synonyms, reviews, definition, history, classification, pathologic anatomy, incidence, pathogenesis, clinical course, complications, diagnosis, prognosis, and therapy. A very worth-while addition under each variety of tumors is a short chapter showing its occurrence in animals, as, for example, "Ovarian Common Carcinomas in Animals." "Ovarian Teratoids in Animals." The avian equivalent of a dermoid, by the way, contains feathers instead of hair!

Endometriosis is included, as it may be considered a neoplasm. In a personal statistical analysis of 160,324 gynecologic patients, the author found that 4,503, or 2.8 per cent, showed ovarian tumors.

This immense accumulation of facts correlated, systematized, concentrated, and presented under the guidance of an exceptionally gifted and industrious scientist is a noteworthy accession to the literature of gynecology and endocrinology.

R. T. FRANK.

Claude Bœlère publishes a large (371 pages) monograph on *Hormonal Diagnosis and Hormonal Therapy in Gynecology*.²³ The introduction is by Simonnet with whom Bœlère has collaborated for years in both laboratory and clinical investigation.

To me, the attempt at innumerable subdivision based on clinical, bio-assay and other criteria has become more and more abhorrent. Realizing the extreme unreliability of various tests, the many incalculable factors, both local and general which enter the picture, I have

²²*Encyclopedia of Endocrinology* by Hans Selye, M.D., Ph.D. (Prague), D.Sc. (McGill), F.R.S. (Canada). Professor and Director of The Institute of Experimental Medicine and Surgery, University of Montreal. Section IV, Ovary. Volume VII. Ed. Ovarian Tumors (Bibliography). 427 pages. Section IV, Ovary. Volume VII. Ovarian Tumors. 289 pages. Richardson, Bond and Wright, Montreal, Canada. 1956.

²³*Diagnostic Hormonal et Traitements Hormonaux en Gynécologie*. Par Claude Bœlère. Préface du Professeur H. Simonnet. 371 pages. Masson et Co., Paris, N° 1946.

any physician who will fail to find at least several essays which will prove of absorbing interest to him. Moreover, the authors have kept their promise in presenting their subject in a fashion understandable to the average physician.

Beadle of Stanford deals with "The Gene and Biochemistry." He emphasizes the similarity of genes and viruses. These basic functional units can be influenced (mutation) and can be used as "tools in determining the course of biosynthesis. . . ." "Viruses," by Stanley of the Rockefeller Institute, are submicroscopic entities which produce proliferative or degenerative changes in the cells they have invaded. These crystallizable nucleoproteins possess an "activity somewhat akin to that possessed by certain protein hormones and enzymes." Gaffron of the University of Chicago, describes "Photosynthesis and the Production of Organic Matter on Earth which makes possible the abundance of living things on the earth." The gap between the demand for and the supply of organic material is diminishing hourly, just as we are cutting down our forests three times as fast as they grow.

It is quite impossible to do justice to this book by even the briefest of reviews. If only I can whet the appetite of the reader sufficiently to make him take up this treat, he will continue of his own accord. The bacterial cell (Dubos); the nutrition and biochemistry of plants (Hoagland); the biological significance of vitamins (Elvehjem); some aspects of vitamin research (Folker); (the elucidation of their chemical constitution in ten years!); quantitative analysis in biochemistry (Van Slyke) (by the father of micromethods); hormones by Houssay; the steroid hormones (Pincus); plant hormones (Thimann); the chemical mechanism of nervous action (Nachmansohn); chemotherapy (Hotchkiss); some biochemical problems posed by a disease of muscle (Hoagland); social aspects of nutrition (Sebrell) are some of the subjects dealt with. The book contains a mine of information.

R. T. FRANK.

Penicillin in Syphilis, by J. E. Moore,²⁹ gives the present status of the agent and its clinical use. The sudden advent of penicillin in wartime brought about an organized investigation into its use in the problem of early syphilis in the armed forces. The result of its continued use in peacetime by a number of cooperating clinics has made available methods and results which are used basically in the text. The pharmacology of the agent, Chapter two, is a detailed account of the various techniques and potencies which have been employed, the nature of the effect on lesions of the various systems, and a discussion of the different species now produced.

Continuing chapters set forth with clarity the mechanism of action of penicillin, the manner in which its use for such infections as gonorrhea may mask the diagnosis of syphilis, and its employment in early, latent, and systemic lesions. The newness of the therapy and its apparently uncertain results in certain lesions have led to a note of caution in several places, as well as an emphasis on the responsibility of the physician who adopts this therapy to carefully follow up and repeatedly observe his patients after penicillin treatment.

The use of penicillin in treatment of the syphilitic pregnant woman forms an extended chapter. Among 76 women with manifest early syphilis so treated, only one infant developed congenital syphilis. In discussing this case, Moore suggests that a larger dose should have been given over a longer period, or that the patient should have been retreated because of lack of serologic response. The total dosage employed in the pregnant syphilitics has varied from 1.2 to 4.8 million units, in a period of eight to fifteen days. The statement appears that penicillin treatment on any stage of pregnancy is effective in preventing congenital syphilis, and again, that a negative serologic test in the mother at the time of delivery is not essential to the birth of a healthy infant. Abortions, reaction phenomena, actual and threatened, among the penicillin-treated syphilitic women do not equal the normally expected incidence of spontaneous abortions in nonsyphilitics. If a mother is apparently

²⁹**Penicillin in Syphilis**, by Joseph Earle Moore, M.D., Associate Professor of Medicine and Adjunct Professor of Public Health Administration, The Johns Hopkins University; Physician-in-charge Syphilis Division of the Medical Clinic and Visiting Physician, The Johns Hopkins Hospital; Chairman, Syphilis Study Section, National Institute of Health, United States Public Health Service; Chairman, Subcommittee on Venereal Disease, National Research Council. 290 pages. Charles C Thomas, Springfield, Illinois. 1946.

chapter on the hormones derived from nonendocrine organs, covering those of the gastrointestinal tract and the still supposititious cardiac, liver, renal, etc., ones.

The value of the chapter bibliographies is somewhat diminished by the author's fondness for singling out reviews and limiting his quotations rather strictly to all literature published during the last ten years. On the whole, this is a very satisfactory and sound presentation of the subject, showing that endocrinology is beginning to reach a more stable status.

R. T. FRANK.

Wallet²⁶ has spent four years in de Gennes' clinic in gathering evidence of hyperestrogenic secretion as well as of hyperluteinization. This elaborate monograph, which quotes 1,220 works from the world's literature, is based largely on endometrial histologic findings (biopsies).

The chemistry, physiologic effects, metabolism, etc., of estrogens is taken up in detail, as is the uterine and vaginal cycle, the role of the hypophysis, the interrelation of the glands. The blood and urine hormone assays are described in detail, but evidently were not employed in this research, which is mainly based on uterine biopsies obtained by the Novak apparatus. Based on these criteria, a very detailed symptomatology, which embraces all the known functional deviations as well as organic lesions such as fibroids and cancer, are viewed from this very onesided and artificial aspect.

R. T. FRANK.

In a more than 300 page monograph, Dr. Jules Samuels describes the **Hormone Maintenance of the Fetus**.²⁷ This same endocrinologist, in 1938, published a pregnancy test by means of spectroscopic examination of the blood, a test which was never regarded seriously by other investigators. I confess that I was unable to read this book with either care or interest, in spite of the fact that it has 544 references to the literature and covers pregnancy not only in the human being, but also in the mare, monkey, cow, rat, pig, and other mammals; likewise pregnancy reactions in human beings and animals. This monograph is supposed to be a part of an as yet uncompleted five volume endocrinology which deals especially with the dysfunction of the hypophysis, its diagnosis and therapy. The author considers the gonadotropic factor a cell activator and in cell division, an accelerator. The thyrotropic factor is an activator of the multiplication rate. He has made studies of the prepituitary and placenta in various animals. Fortunately, there is a summary at the end of the book in four different languages. To read even the English summary, which covers 18 pages, proves an arduous task and has in no way clarified my concepts of this rather involved question. Whether it will prove of any use to special investigators on the subject, I must leave to their own judgment.

R. T. FRANK.

Miscellaneous

Currents in Biochemical Research,²⁸ edited by David E. Green, is a most unusual and intriguing book. Under one cover, thirty-one well-known investigators have described "in as simple language as possible" the important developments in their own field. The scope is immense, covering pharmacology, chemotherapy, public health, genetics, photosynthesis, and agriculture, viewed from the organic analytical and physical chemistry angles. I do not say that every reader will study each article with equal care, but I cannot conceive of

²⁶*L'Hyperfolliculaire. Étude Clinique, Anatomopathologique et Thérapeutique.* Par Max Wallet. Préface de L. De Gennes. 354 pages. Masson et Cie, Paris (VIe). 1946.

²⁷*Die Hormonversorgung des Fetus.* von Dr. Jules Samuels, Chirurg Frauenarzt, Spezial Arzt für endogene Endokrinotherapie, Amsterdam. 320 pages. E. J. Brill, Lieden. 1947.

²⁸*Currents in Biochemical Research.* Edited by David E. Green. Thirty-one essays charting the present course of Biochemical Research and considering the intimate relationship of Biochemistry to medicine, agriculture and social problems. 486 pages. Interscience Publishers, Inc., New York. 1946.

insulin in diabetes, the book offers a full and clear discussion of recent research and clinical experience.

The value of prophylactic postoperative treatment was demonstrated in a series of gynecologic cases at Stockholm. The material selected was known to give a high frequency of thrombosis. In 140 cases the dosage, 50 + 50 + 100 mg. daily as recommended by Crafoord, was given. There was one thrombosis. In approximately 100 other cases in the series the dosage was 50 + 50 + 50 mg. Two patients had thrombosis, both had sepsis, and one died of sepsis. In the maternity at Lund a serious uterine hemorrhage in an early postpartum treatment series caused the drug to be withheld until from twelve to twenty-four hours after delivery. In a series of cases, 50 + 50 + 100 mg. dosage, there were two cases of late thrombosis, nineteenth day post partum. The author regards a routine and sufficiently prolonged therapy with heparin as giving almost complete protection against thromboembolic complications after surgical operations and childbirth. The author feels the use of dicoumarol, which is fully discussed, has a markedly specific therapeutic effect in thrombosis. Surgery of thrombosis, therapeutic ligation, early ambulation, and many other aspects of the problem are discussed in this valuable book.

PHILIP F. WILLIAMS.

Chronic Disease and Psychological Invalidism,³² A Psychosomatic Study, has been written by Jurgen Ruesch, with a collaborating staff, and appears from the Division of Psychiatry, University of California Medical School and the Langley Porter Clinic, San Francisco. The monograph deals particularly with the psychologic system, economic and cultural determinants during convalescence, and their influence upon speed and degree of recovery. Since neither psychological, anatomic, and pathologic factors are entirely useful in determining a complete state of recovery, the author group have used a psychosomatic approach in a group of 187 cases of delayed recovery.

These cases have been identified according to the general characteristics of the population, various indices of adjustment, life habits, and the histories of social relationships and measurement of their personalities and intelligence, in which the Minnesota "Multiphasic Personality Inventory" was found most suitable. There are sections on medical aspects, psychosomatic relations, situational conflicts, and character problems. In these discussions there is much to interest the gynecologist in regard to the "operation hungry" patient, multiple castration, frigidity, abortion, and loss of menstruation. The authors note the simultaneous occurrence of psychological problems and of disease in 73 per cent of their delayed recovery cases. Again, of interest to the gynecologist is the study of the psychologic conflicts present in many of their patients in the nature of forced separation, divorce, childbirth, and widowhood. Such changes in the intimate human environment at the onset of the disease in which recovery did not occur happened in 45 per cent of the cases. The chapter on psychological problems in general medicine merits reading by all physicians. The situation of the "perpetually referred" patient is analyzed.

The authors have discussed the prognosis in the delayed recovery type of case, and note how some may be selected for therapy. While individual therapy is regarded as of advantage to most such patients, it is felt that many of these individuals after short primary individual therapy could be more advantageously treated as a group. The intricate psychological background of many gynecologic problems, as Deutsch has pointed out, necessitates as thorough consideration and therapy as the surgical treatment which may seem to be indicated. Probably in many of these individuals a consultation with a psychiatrist may benefit the patient as effectively as surgery.

PHILIP F. WILLIAMS.

³²**Chronic Disease and Psychological Invalidism, A Psychosomatic Study.** By Jurgen Ruesch, M.D., in collaboration with Robert E. Harris, Ph.D., Carole Christiansen, M.A., Susanne H. Heller, B.A., Martin B. Loeb, B.A., Sally Dewees, M.S., Annemarie Jacobson, M.D., with a foreword by Karl M. Bowman, M.D., from the Division of Psychiatry, University of California Medical School and the Langley Porter Clinic, San Francisco. 191 pages. Published with the Sponsorship of The American Society for Research in Psychosomatic Problems, New York, 1946.

cured of her own infection in her first pregnancy she should, according to Moore, be re-treated in each subsequent pregnancy. The results of penicillin in pregnancy infections have compared very favorably with the results by arsenicals and the heavy metals. The abandonment of these latter therapies is recommended. A standard follow-up of infant and mother is suggested.

There is a short concluding chapter on streptomycin. On the basis of recorded observations, Moore states that streptomycin is unlikely to prove clinically useful in syphilis. The first half of this book is basic, and should be read by all who treat syphilis with penicillin. The last part of the book is a splendid exposition of present-day therapy with this antibiotic.

PHILIP F. WILLIAMS.

In this account of **Radical Surgery in Advanced Abdominal Cancer**³⁰ Dr. Brunschwig details the operative technique of many of the 100 such cases which form the subject of his report. The radical attack upon this seemingly hopeless and apparently inoperable group in an effort to afford them a certain degree of palliation produced a truly amazing salvage of 19 patients who survived the massive resections from two to ten years. It would appear from the favorable results obtained in many of these cases, Chapter Three, that too great consideration for medical contraindications should not prevent exploratory laparotomy for advanced abdominal cancer. The chapter on preparation of such cases for operation brings out the fullest application of the advances of recent research on shock, anesthesia, biochemistry, nutrition, and chemotherapy. As described in the chapter on supportive treatment, one can agree that the fullest use of such measures must modify the previous concepts of operability. The sections of the nutritive state in relation to protein metabolism and on parenteral nitrogenous nutrition discuss fully the expanding use and efficiency of such methods of nutrition.

The various, and usually multiple, operations for cancer arising in the stomach, small intestine, colon, pancreas, liver, and bile ducts, as well as a discussion of the treatment of injuries to vessels and operations on the spleen and adrenal glands, form the subject matter of fourteen chapters.

Probably the readers of this JOURNAL may be more interested in the author's remarks on the treatment of intra-abdominal extension of gynecologic cancer, than some of the preceding topics. Certainly a reading of these case reports makes one feel that such extensive resections often may be of value in the case regarded as hopeless. In a discussion of the complications following irradiation therapy, obstruction of the intestines or radiation ulcers, the author points out that many such cases should not at once be regarded as recurrent carcinoma. The evidence of 30 per cent palliation and 19 per cent prolonged survival indicates the need for a more radical attitude toward advanced abdominal cancer by those qualified to attempt such surgery.

PHILIP F. WILLIAMS.

This monograph **Heparin in the Treatment of Thrombosis** by J. Erik Jorpes,³¹ who has done outstanding research on the subject, presents a detailed account of the chemistry and physiology of heparin, and the accumulated experience with this agent in the treatment of thrombosis. There are also extended sections on the nature and use of dicoumarol, as well as a discussion of the pathogenesis of thrombosis and its social aspects. Learmonth, in this foreword, in remarking on the prevalence of thrombo-embolic conditions in peacetime in all countries, states that in Sweden it is a particularly formidable problem. To those interested in any aspect of this anticoagulant, now regarded as specific in thrombosis as

³⁰**Radical Surgery in Advanced Abdominal Cancer**, by Alexander Brunschwig, M.D., Professor of Surgery, University of Chicago. 318 pages. With 11 illustrations. The University of Chicago Press, Chicago, Illinois. 1947.

³¹**Heparin in the Treatment of Thrombosis, An Account of Its Chemistry, Physiology, and Application in Medicine**, by J. Erik Jorpes, M.D., Reader in Biochemistry, The Caroline Institute, Stockholm, Sweden, with a foreword by J. H. Learmonth, C.B.E., Ch.M., F.R.C.S.D., Professor of Surgery, University of Edinburgh. Second Edition. 257 pages. Illustrated. Oxford University Press, London, New York, Toronto. 1946.

The U. S. Pharmacopeia. The thirteenth edition of this monumental work has recently been issued by the authority of the U. S. Pharmacopeial Convention and is official from April 1, 1947.³⁶ First published in 1820, the history of its further progress constitutes an important chapter in American medical annals. The Pharmacopeia is a therapeutic guide to the profession, it presents a review of the progress in medicine and surgery progress from a critical and unbiased evaluation emanating from authoritative sources, and the preparations listed are prepared in accordance with accepted official standards of quality, purity, and strength. The inclusion of the various glandular products, vitamins, antibiotics, sulfa drugs, etc., constitutes valuable information for the gynecologist and obstetrician.

GEO. W. KOSMAK.

The continued and expanding teaching of sex education in schools and other institutions where young people are brought together necessitates an educational service for those who must do the teaching. This small volume, "Sex Education, A Guide for Parents, Teachers, and Youth Leaders," by Cyril Bibby³⁷ gives ample material for those to whom such education is entrusted. The author discusses in early chapters the responsibility of such teaching, the receptive age, the amount and nature of the instruction in relation to the questions of childhood, and the growing interest in domestic biology in the school child. The psychology of adolescence and the teaching of normal reproductive biology to high school and college students are described.

For those in whose hands such instruction is placed, parents, teachers, physicians, nurses, there is much of practical value in the six appendices as to education methods from the toddler, asking where the new baby came from, to the young man and woman who seek information on marriage hygiene and family planning.

PHILIP F. WILLIAMS.

³⁶The Pharmacopeia of the U. S. of America. Thirteenth Edition. Including supplements when issued. Easton, Pennsylvania, Mack Printing Company, 1947.

³⁷Sex Education: A Guide for Parents, Teachers and Youth Leaders. By Cyril Bibby, M.A., M.Sc., F.L.S., Education Officer to the Central Council for Health Education. 311 pages. Emerson Books, Inc., New York. 1946.

Dr. Spies details his **Experiences With Folic Acid**³³ in the treatment of anemias. He has found that the anemias which respond are the macrocytic diseases—pernicious anemia of Addison's; sprue, both tropical and nontropical; and the nutritional macrocytic anemias including those of pregnancy and pellagra. Just how he got particularly interested in the triad of folic acid is somewhat involved and unclear. He states that in some liver extracts, folic acid was discarded early in the preparation and yet these extracts were active. Nevertheless Spies tried the folic acid. In order to have an ample material, patients in Cincinnati, in the Nutrition Clinic of Birmingham, Alabama, in hospital from Havana, and in the Institute for Tropical Diseases of Puerto Rico were treated.

A very detailed account of the history taking and the minute and extensive physical examination is given, including particularly neurological and blood tests. One of the main differences between the Addisonian pernicious anemia and nutritional macrocytic anemia is that in the latter there is present free gastric hydrochloric acid. The author states that the results obtained with synthetic folic acid are almost incredible. Two hundred eighteen cases were studied. The leucopenias due to arsenic, sulfa, and aminopyrine do not respond to this form of therapy. There appears to be little doubt that the active substance in liver extract is not folic acid but a much more powerful factor, as yet not purified. The therapy consists not only in the usual methods of rest, adequate nutrition, but in addition some 20 mg. of folic acid per day. The monograph is very detailed in its diagnostic and therapeutic description and proves very interesting and worth-while reading.

R. T. FRANK.

Minder has written a **Textbook of Urology**³⁴ while stranded in Zürich by the war. He had previously functioned as professor of urology and director of the Urological University Clinic in Budapest. The book is written in the form of 25 lectures designed particularly for students and practitioners. It does not make an appeal to the specialist. Like similar books from the same publishing firm, it is gotten out faultlessly. It has side indices to make reference easy. For a book of its kind, the number of illustrations is distinctly sparse (62) and many of them diagrammatically simplified. This is a very thorough, complete and up-to-date presentation, which, however, has little to offer to the American student who has so many textbooks at his disposal.

R. T. FRANK.

The standard **Atlas of Human Anatomy**³⁵ originally published by Carl Toldt and adapted by M. Eden Paul which first appeared in 1919 and which in its first and second editions has been republished nine times, is now again available in its tenth incarnation.

It almost is tautologous to describe this well-known textbook consisting mainly of some 1,500 clearly drawn anatomical figures, many in two or more colors, with captions underneath each figure. A vast amount of additional information is contained in the many page footnotes in small print, as well as in the three appendices in Vol. II (567 in number). English, American and International terminology appears in each figure. It is good to have this old and trusty counsellor again available.

R. T. FRANK.

³³**Experiences With Folic Acid.** By Tom D. Spies, M.D., Associate Professor of Medicine, University of Cincinnati School of Medicine; Director of the Nutrition Clinic, Hillman Hospital, Birmingham, Alabama. 110 pages. The Year Book Publishers, Inc., Chicago. 1947.

³⁴**Lehrbuch Der Urologie** von Prof. Dr. Med. J. Minder, ehem. Ordinarius für Urologie und Direktor der Urolog. Universitäts-Klinik Budapest zur Zeit Spezialarzt der Urologie in Zürich. 548 pages. Hans Huber, Bern, Switzerland. 1946.

³⁵**An Atlas of Human Anatomy.** For Students and Physicians. By Carl Toldt, M.D., assisted by Professor Alois Vella Rossi, M.D. Adapted to English and American and International Terminology by M. Eden Paul, M.D., Brax., M.R.C.S., L.R.C.P. Volume I.—Second Edition. Containing Sections on Regions of Human Body, Osteology, Arthrology, Myology (Figures 1 to 649, and General Index to the two volumes). 359 pages. Volume II.—New Second Edition. Containing Sections on Splanchnology, Angiology, Neurology, Organs of the Senses (Figures 651 to 1505, with Appendices, and General Index to the two volumes). 622 pages. The Macmillan Company, New York. 1944.

a trace of muscle adenylic acid in $n/10$ sulfuric acid. The final pH was 7.3. The mixture was incubated at 37°C . for one hour and then examined for P_o . Control tests were run on enzyme-blank and substrate-blank reaction mixtures.

Purified extract of a secretory endometrium, taken from a myoma patient in the twenty-second day of the cycle, failed to mediate hydrolysis of glycerophosphate, but liberated 0.14 mg. P_o from Cori ester in the conditions described. It may be concluded, therefore, that the extract contained some phosphorylase. A second examined secretory endometrium specimen behaved similarly.

On the other hand, extracts from two proliferative endometrium specimens failed to liberate P_o from Cori ester in the test conditions which have been described, and were therefore entirely lacking in any phosphorylase activity.

2. Phosphorolysis of glycogen by homogenates of endometrium.—Specimens of human endometrium were tested for phosphorolysis activity on glycogen as follows: the cooled tissue material, at arrival in the laboratory within roughly fifteen minutes from the time of curetting, was rinsed once with saline solution to remove adhering blood, blotted with filter paper to remove excess saline, and minced in a chilled dish. Two hundred milligrams of mince was added to 1.0 ml. of a phosphate Ringer mixture in which 1 or 5 per cent glycogen and $m/40$ sodium fluoride were included. The phosphate Ringer had the following composition: 4 ml. potassium chloride, 1.15 per cent; 1 ml. magnesium sulfate, 0.8 per cent; 100 ml. sodium chloride, 0.9 per cent; 60 ml. $m/10$ phosphate buffer of pH 7.4. Fluoride was included in the mixture to ensure that masking of phosphorolysis by secondary reactions of dephosphorylation would not occur. The suspension was shaken at 37°C . for two hours. Reaction was stopped with 0.5 ml. of 20 per cent trichloroacetic acid. After addition of 5.0 ml. water, the suspension was filtered. P_o was determined promptly in an aliquot of the filtrate. The amount of P_o present at the beginning of the incubation period was determined in parallel control tests. The found decrease in P_o was expressed in per cent of P_o added at the outset.

Demonstration of phosphorolysis activity by this method proved to be dependent on the use of a sufficient excess of glycogen in the test mixture. When the glycogen level was low (1 per cent), several tested secretory specimens failed to mediate a measurable decrease of the phosphate level. When, however, the glycogen content of the test mixtures was increased to 5 per cent, homogenates prepared from the secretory type specimens caused uniformly, as may be seen in Table I, a definite decrease of inorganic phosphate ($-\Delta \text{P}_o = 11 - 18\%$). All tested proliferative type (six intermenstrual and three anovulatory cycle premenstrual) specimens, on the other hand, showed lower or even insignificant phosphorolysis activity in the same conditions ($-\Delta \text{P}_o = 0 - 9\%$).

The data which have been set forth indicate first that progestational human endometrium contains phosphorylase, and, second, that the phosphorolysis activity of endometrium as measured in a homogenate of the tissue rises markedly as the endometrium progresses from proliferation to secretion. It may be recalled that Hughes⁶ has demonstrated the presence in human endometrium of an amylase system and has shown that this system, too, increases in activity during progestational growth.

The enzyme systems of endometrium which act on glycogen—phosphorylase and amylase—therefore vary cyclically in their activity in parallel to the glycogen content of the tissue. It is tempting to speculate on a casual relation between them. In this connection a sequence of the following form deserves consideration: phosphorylase \rightarrow glycogen \rightarrow amylase. The increase in phosphorylase activity during progestation is a self-evident cause of the increase in glycogen during this phase of the cycle. Of the increase of amylase activity during progestation, it can be supposed that it is in the nature of an adaptive or compensatory response to the glycogen rise.

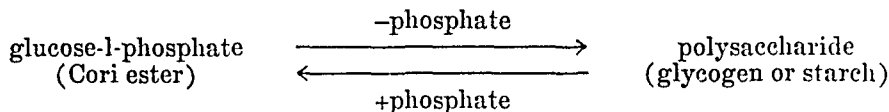
The two different glycogen-oriented enzyme systems of endometrium do not duplicate the same function, but are mutually complementary. Phosphorylase in the endometrium is a synthesizing instrument. By its means the endometrium fixes diffusible sugar and retains it in the form of a nondiffusible and hence storable reserve stuff (glycogen). On the other

Correspondence

Phosphorylase Activity in Human Endometrium

To the Editor:

It is now well known¹ that production of glycogen in the major glycogen depots (muscle, liver) is mediated by an enzyme phosphorylase which catalyzes a reversible equilibrium of the following general form:



Direct evidence has not hitherto been adduced, however, for the operation of this system in an important glycogen depot tissue of the female reproductive tract, the secretory uterine mucosa.

Abundant stores of glycogen are deposited in the gland cells of primate endometrium (human, macaque) during the progestational (secretory) phase of a normal menstrual cycle. It is found, however, that in a condition "glycopenia uteri," which is associated with sterility, the endometrium, although anatomically of the progestational type, is poor in glycogen as compared to the normal.^{2, 3} The possibility arises that glycogen of secretory endometrium is designed to play a specific role in the maintenance of the life of the fertilized ovum. In view of this conjecture, and in consideration of the diagnostic importance of glycogen in the examination of the causes of infertility, information concerning the enzyme basis of glycogen production in human endometrium was felt to be desirable.

The specimens of endometrium were taken by curetting from 20- to 40-year-old women with diagnosis of uterine myoma or complaint of infertility, and who had reported normal menstrual cycles. The tissue was obtained in the operating room and sent to the laboratory in a dish over ice. A small sample was set aside for histologic analysis, and the remainder was used for the enzyme tests. The interval from curetting until analysis of enzyme activity was about fifteen minutes.

Phosphorylase activity was ascertained according to methods which have been described in connection with a survey of phosphorylase in rat tissues by Shapiro and Wertheimer.⁴ Phosphate was determined according to Sumner⁵ with a Pulfrich photometer set at filter S61.

In the presence of a strong amylase activity, the conversion of Cori ester into glycogen by an extract cannot be expected to lead to an actual accumulation of glycogen in the solution. Phosphorylase activity in such a case should nevertheless leave its mark in terms of: (a) a liberation of inorganic phosphate (P_0) in a medium containing Cori ester; (b) a decrease of inorganic phosphate (P_0) by interaction with glycogen in mixtures which contain a sufficient excess of the latter. A method based on (a) was employed to investigate the phosphorylase activity of endometrium in a group of four cases. A method based on (b) was employed in a series comprising a total of 16 cases.

1. *Effect of extract of endometrium on Cori ester.*—These experiments included tests on two secretory and two proliferative specimens. The technique was as follows: The fresh tissue was minced and extracted for thirty minutes in the cold with an equal weight of water. The filtrate was purified by adsorption on alumina gel and elution in a solution of glycerophosphate according to the procedure of Shapiro and Wertheimer.⁴ A test mixture was made of 1 ml. purified extract (volume of eluate equivalent to 1 Gm. fresh tissue) and 0.5 ml. of a substrate mixture in which was contained 3 per cent Cori ester, 1.5 per cent glycogen, and

Item

American Congress on Obstetrics and Gynecology

Three panel-type morning sessions on the following subjects have been arranged:

1. *Anesthesia and Analgesia*, Tuesday, September 9, Dr. Nicholas J. Eastman, Chairman, with the cooperation of Dr. J. P. Greenhill, Chicago; Dr. John Adriani, New Orleans; Dr. Stuart Cullen, Iowa City; and Dr. Arthur Baptisti, Hagerstown.

2. *Cancer*, Wednesday, September 10, Dr. Robert A. Kimbrough, Philadelphia, Chairman, with the cooperation of Dr. John Randall, Iowa City; Dr. Charles L. Martin, Dallas; Dr. Joe V. Meigs, Boston; and Dr. Herbert Schmitz, Chicago.

3. *Cesarean Section* on Thursday, September 11, Dr. Edward Schumann, Philadelphia, Chairman, with the cooperation of Dr. Edward G. Waters, Jersey City; Dr. Edward Davis, Chicago; Dr. E. D. Plass, Iowa City; and Dr. William Benbow Thompson, Hollywood.

The afternoon meetings of the Medical Section of the Congress will consider the Psychosomatic Aspects of Pregnancy on Tuesday; Pregnancy Complicated by Heart Disease, Diabetes, and Tuberculosis on Wednesday; and Recent Advances in Endocrinology on Thursday.

Round table discussions from 4:00 to 5:00 P.M. daily will consider such topics as abortions, asphyxia, fibroids, prolonged labor, infertility, early ambulation, uterine bleeding, nutrition in pregnancy, endometriosis, the Rh factor, erythroblastosis, geriatric gynecology, and other pathologic conditions relating to obstetrics and gynecology.

Concurrent round table sessions will be held for nurses, hospital administrators, and public health workers.

A scientific and educational exhibit under the direction of Dr. J. P. Pratt of Detroit and a comprehensive motion picture program under the guidance of Dr. John Parks of Washington are in process of development. Those wishing to make applications for space in these exhibits, especially for time on the cinema program, are urged to make early application. Necessary blanks may be obtained from the office of the Congress, 24 West Ohio Street, Chicago 10, Illinois. Better hurry!

On Friday, the last day of the Congress, the entire morning will be given over to the program of the National Federation of Obstetric-Gynecologic Societies. Dr. James S. Taylor of Altoona is arranging this session.

TABLE I. PHOSPHOROLYSIS OF GLYCOGEN BY ENDOMETRIUM TAKEN IN DIFFERENT STAGES OF THE MENSTRUAL CYCLE

| CASE | DAY IN CYCLE | COMPLAINT | FOUND DECREASE OF INORGANIC PHOSPHATE IN PER CENT OF INITIAL VALUE |
|--|--------------|-----------|---|
| <i>I. Secretory Premenstrual Specimens</i> | | | |
| 1 | 18 | Myoma | 12 |
| 2 | 21 | — | 18 |
| 3 | 24 | — | 11 |
| 4 | 25 | — | 15 |
| 5 | 27 | Sterility | 14 |
| 6 | 27 | Sterility | 14 |
| 7 | 27 | Sterility | 16 |
| <i>II. Proliferative Intermenstrual Specimens</i> | | | |
| 8 | 8 | Myoma | 9 |
| 9 | 9 | Myoma | 2 |
| 10 | 11 | Myoma | 5 |
| 11 | 11 | Sterility | 0 |
| 12 | 12 | Myoma | 1 |
| 13 | 16 | Myoma | 1 |
| <i>III. Proliferative Premenstrual (anovulatory cycle) Specimens</i> | | | |
| 14 | 24 | Sterility | 4 |
| 15 | 25 | Sterility | 9 |
| 16 | 28 | Sterility | 5 |

hand, amylase can only serve in an opposite capacity. By means of amylase the tissue is able to mobilize its glycogen reserve and convert it into sugars (maltose, glucose) which can diffuse through the membrane of the cell. Amylase is thus important in endometrium probably because it enables this tissue to put its accumulated depot of carbohydrate at the disposal of the invading ovum.

The following summary may be presented:

1. Human endometrium contains phosphorylase.

2. A marked rise in the phosphorylase activity of endometrium accompanies progestation. This rise accounts for the deposition of glycogen in endometrium during its progestational phase.

3. A division of physiologic function between the two glycogen-oriented enzyme systems—phosphorylase and amylase—of endometrium, and a possible mutual connection between them in their increase during progestation are discussed.

BERNHARD ZONDEK, M.D.
SHILOMO HESTRIN, PH.D.

GYNECOLOGICAL-OBSTETRICAL DEPT.
ROTHSCHILD-HADASSAH UNIVERSITY HOSPITAL
HORMONE RESEARCH LABORATORY, HEBREW UNIVERSITY
JERUSALEM, PALESTINE
FEBRUARY 16, 1947.

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1. Cori, C.: *Endocrinology* 26: 285, 1940.
2. Zondek, B., and Stein, Z.: *Endocrinology* 27: 395, 1940.
3. Zondek, B., and Shapiro, B.: *AM. J. OBST. & GYNEC.* 44: 345, 1942.
4. Shapiro, B., and Wertheimer, E.: *Biochem. J.* 37: 397, 1943.
5. Sumner, G.: *Science* 100: 413, 1944.
6. Hughes, E.: *AM. J. OBST. & GYNEC.* 49: 10, 1945.

- St. Louis Gynecological Society.** (1924) *President*, Otto Krebs. *Secretary*, John E. Hobbs, 630 S. Kingshighway, St. Louis, Mo. Meetings second Thursday, October, December, February, and April.
- San Francisco Gynecological Society.** (1929) *President*, Albert M. Vollmer. *Secretary*, Daniel G. Morton, University of California Hospital, San Francisco, Calif. Regular meetings held second Friday in month from October to April, University Club, San Francisco, or Claremont Country Club, Oakland, Calif.
- Texas Association of Obstetricians and Gynecologists.** (1930) *President*, T. F. Bunkley. *Secretary*, J. McIver, 714 Medical Arts Bldg., Dallas, Tex.
- Michigan Society of Obstetricians and Gynecologists.** (1924) (Formerly the Detroit Obstetrical and Gynecological Society.) *President*, Clarence E. Toshach. *Secretary*, John P. Ottaway, 1551 Woodward Ave., Detroit, Mich. Meetings first Tuesday of each month from October to May (inclusive).
- Central New York Association of Obstetricians and Gynecologists.** (1938) *President*, Edward C. Hughes. *Secretary*, Nathan N. Cohen, 713 E. Genesee St., Syracuse, N. Y. Meets second Tuesday of September, November, January, March, and May.
- Alabama Association of Obstetricians and Gynecologists.** *President*, Gilbert F. Douglas. *Secretary*, Hunter Brown, 1922 South Tenth Ave., Birmingham, Ala.
- San Antonio Obstetric Society.** *President*, I. T. Cutter. *Secretary*, S. Foster Moore, Jr., San Antonio, Tex. Meetings held first Tuesday of each month at Gunter Hotel.
- Seattle Gynecological Society.** (1941) *President*, Carl M. Helwig. *Secretary*, Roger E. Stewart, Stimson Bldg., Seattle, Wash. Meetings held on third Wednesday of each month.
- Denver Obstetrical and Gynecological Society.** (1942) *Secretary*, Emmett A. Mechler, 1612 Tremont St., Denver, Colo.
- Wisconsin Society of Obstetrics and Gynecology.** (1940) *President*, J. M. Freeman. *Secretary-Treasurer*, Lionel T. Servis, 425 East Wisconsin Ave., Milwaukee. Meetings held in May and October.
- San Diego Gynecological Society.** (1937) *President*, R. C. Hall. *Secretary*, D. Dalton Deeds, 2001 Fourth Ave., San Diego, Calif. Meetings held on the last Wednesday of each month.
- North Dakota Society of Obstetrics and Gynecology.** (1938) *President*, Ralph E. Leigh, Grand Forks. *Secretary*, G. Wilson Hunter, 807 Broadway, Fargo, N. D.
- Virginia Obstetrical and Gynecological Society.** (1936) *President*, S. E. Oglesby. *Secretary*, L. L. Shamburger, 628 State Office Bldg., Richmond 19, Va. Next meeting not announced.
- Columbus Obstetrical and Gynecological Society.** (1944) *President*, Wynne M. Silbernagel. *Secretary*, Zeph J. R. Hollenbeck, 9 Buttles Ave., Columbus, Ohio. Meetings held fourth Wednesday of each month.
- Naussau Obstetrical Society.** (1944) *President*, Austin B. Johnson. *Secretary*, Robert S. Millen, Westbury, N. Y. Meetings, bimonthly from October to May.
- Bronx Gynecological and Obstetrical Society.** (1924) *President*, George Muscillo. *Secretary*, Milton D. Klein, 1882 Grand Concourse, New York 57, N. Y. Meetings, fourth Monday monthly from October to May.
- Washington State Obstetrical Society.** (1936) *President*, John H. Fiorino, Everett. *Secretary*, H. H. Skinner, Yakima, Meetings, first Saturday of April and October.
- Kansas City Obstetrical and Gynecological Society.** (1922) *President*, Thomas J. Sims. *Secretary*, LeRoy Goodman, 702 Bryant Bldg., Kansas City, Mo. Meetings, last Thursday, September, November, January, and March; first Thursday, May, University Club.
- Los Angeles Obstetrical and Gynecological Society.** (1914) *President*, George E. Judd. *Secretary*, Carl E. Krugmeier, 2200 West Third Street, Los Angeles, Calif.
- North Carolina Obstetrical and Gynecological Society.** (1932) *President*, Wallace B. Bradford. *Secretary*, Richard B. Dunn. Meetings semiannually.
- The Society of Obstetricians and Gynecologists of Canada.** (1944) *President*, William A. Scott. *Secretary*, James Goodwin, 516 Medical Arts Bldg., Toronto, 5. Meetings held annually, date of next meeting to be announced later.
- Akron Obstetrical and Gynecological Society.** (1946) *President*, L. L. Bottsford. *Secretary-Treasurer*, N. E. Wentsler, 1029 Second National Bldg., Akron 8, Ohio.
- Minnesota Society of Obstetrics and Gynecology.** *President*, L. M. Randall. *Secretary*, Russell J. Moe, 205 West Second St., Duluth, Minn. Meetings held spring and fall.
- Miami Obstetrical and Gynecological Society.** (1946) *President*, M. C. Wilson. *Secretary*, George A. Mitchell, Huntington Bldg. Meetings, second Thursday in January, March, May, and November.
- Omaha Obstetrical and Gynecological Society.** (1947) *President*, M. E. Grier. *Secretary*, B. V. Reaney, 1116 Medical Arts Bldg., Omaha 2, Neb. Meetings held third Wednesday in January, March, May, September, November.
- Oklahoma City Obstetrical and Gynecological Society.** (1940) *President*, Le Roy H. Sadler. *Secretary-Treasurer*, John W. Records, 301 Northwest 12 Street, Oklahoma City.
- Cleveland Obstetrical and Gynecological Society.** (1947) *President*, Robert E. Faulkner. *Secretary*, G. Keith Folger, 10515 Carnegie Ave. Meetings on fourth Tuesday of September, November, January, March, and May at University Club, 3813 Euclid Ave., Cleveland 15, Ohio.

ROSTER OF AMERICAN OBSTETRICAL AND GYNECOLOGICAL SOCIETIES*

(Appears in January, April, July, October)

- American Gynecological Society.** (1876) *President*, Emil Novak, Baltimore, Md. *Secretary*, Norman Miller, Ann Arbor, Mich. Annual meeting to be announced.
- American Association of Obstetricians, Gynecologists and Abdominal Surgeons.** (1888) *President*, A. D. Campbell, Montreal, Quebec. *Secretary*, James R. Bloss, 418-11th Street, Huntington, W. Va. Annual meeting Hot Springs, Va., Sept. 4-6, 1947.
- Central Association of Obstetricians and Gynecologists.** (1929) *President*, Earl C. Sage, Omaha, Neb. *Secretary-Treasurer*, John I. Brewer, 104 South Michigan Ave., Chicago, Ill. Annual meeting Louisville, Ky., Oct. 23, 24, and 25, 1947.
- South Atlantic Association of Obstetricians and Gynecologists.** (1938) *President*, J. Randolph Perdue, Miami, Fla. *Secretary*, E. D. Colvin, 1259 Clifton Road, N.E., Atlanta, Ga. Annual meeting at Augusta, Ga., February 12 to 14, 1948.
- A. M. A. Section on Obstetrics and Gynecology.** *Chairman*, William F. Mengert, Dallas, Texas. *Secretary*, A. B. Hunt, Mayo Clinic, Rochester, Minn. Annual meeting June, 1947.
- New York Obstetrical Society.** (1863) *President*, Albert H. Aldridge. *Secretary*, R. G. Douglas, 530 East 70th St., New York City. Second Tuesday, from October to May, Yale Club.
- Obstetrical Society of Philadelphia.** (1868) *President*, John B. Montgomery. *Secretary*, James P. Lewis, 1930 Chestnut St., Philadelphia, Pa. First Thursday, from October to May.
- Chicago Gynecological Society.** (1878) *President*, Ralph A. Reis. *Secretary*, Herbert E. Schmitz, 25 East Washington St., Chicago 2, Ill. Third Friday, from October to June, Hotel Knickerbocker.
- Brooklyn Gynecological Society.** (1890) *President*, Alexander E. Dunbar. *Secretary*, William T. Daily, 142 Joralemon St., Brooklyn, N. Y. First Friday, from October to May, Kings County Medical Society, 1313 Bedford Ave., Brooklyn, N. Y.
- Baltimore Obstetrical and Gynecological Society.** (1929) *President*, Lawrence Wharton. *Secretary-Treasurer*, John W. Haws, 9 E. Chase St., Baltimore, Md. Meets quarterly at Maryland Chirurgical Faculty Bldg.
- Cincinnati Obstetrical Society.** (1876) *President*, Carroll J. Fair. *Secretary*, Joseph G. Crotty, 136 West McMillan St., Cincinnati, Ohio. Third Thursday of each month.
- Louisville Obstetrical and Gynecological Society.** *President*, Samuel S. Gordon. *Secretary*, J. B. Marshall, 605 Brown Bldg., Louisville, Ky. Meetings at the Brown Hotel every fourth Monday, from September to May, excluding December.
- Portland Society of Obstetrics and Gynecology.** *President*, Ronald Frazier. *Secretary-Treasurer*, Gifford D. Seitz, 919 Taylor St. Bldg., Portland 5, Ore. Meetings last Wednesday of each month.
- Pittsburgh Obstetrical and Gynecological Society.** (1934) *President*, Charles J. Barone. *Secretary*, Eugene A. Conti, 519 North Highland Ave., Pittsburgh 6, Pa. First Monday of October, December, February, April, and June.
- Obstetrical Society of Boston.** (1861) *President*, Frederick J. Lynch. *Secretary*, Paul A. Younge, 1101 Beacon Street, Brookline, Mass. Third Tuesday, October to April, Harvard Club.
- New England Obstetrical and Gynecological Society.** (1929) *President*, Arthur E. G. Edgelow, Springfield, Mass. *Recorder*, Carmi R. Alden, 270 Commonwealth Ave., Boston 16, Mass. Meetings held in May and December.
- Pacific Coast Obstetrical and Gynecological Society.** (1931) *President*, Henry N. Shaw. *Secretary-Treasurer*, William Benbow Thompson, 6253 Hollywood Blvd., Los Angeles, Calif. Next meeting in Seattle, Wash., Oct. 1 to 4, 1947.
- Washington Gynecological Society.** (1933) *President*, Lawrence Lee Cockerille. *Secretary*, Raymond T. Holden, 3111 16 Street, N.W., Washington 10, D. C. Fourth Saturday, October, November, January, March, May.
- New Orleans Obstetrical and Gynecological Society.** (1924) *President*, Eugene H. Countiss. *Secretary*, Joseph W. Reddoch, Pere Marquette Bldg., New Orleans, La. Meetings held October, November, January, March, and May.

*Changes, omissions, and corrections should be addressed to the Editor of the JOURNAL. The number after the Society's name is the year of founding.

addition to the educational publicity given the signs of uterine cancer, which resulted in patients with cancer coming in earlier stages, there has been increasing recognition of the fact that chronic irritation is a predisposing factor and that it should be removed, and that examinations are advisable to detect it while a simple and easily-cured condition. These efforts have dealt principally with carcinoma of the cervix uteri, and in that particular have rendered splendid service, and the removal of chronic cervicitis before cancer develops is gradually spreading throughout the profession in the daily care of patients.

Incidentally, in removing chronic cervicitis, it is important to remove the affected tissue in a way which permits of microscopic check of all of it. The preferable plan is conization. The special electrode, extending the Hyams conization to removal of extensive cervicitis, was devised and reported in 1935.¹⁻² Where conization facilities are not available, conical excision with a knife removes the tissue in a condition permitting thorough microscopic check. But to destroy the affected tissue by cauterization or coagulation, which precludes complete microscopic check, is to invite the risk of overlooking an early cancer. What appears to be simple cervicitis may harbor an area of beginning carcinoma with no indication on the surface of what is going on underneath. A specimen excised before cauterization or coagulation is not sufficient, for the microscopic cancer may be in another part of the affected area.

That removal of cervicitis does really prevent cancer is shown by available statistics. Craig³ found that in 2,895 cases of cervicitis treated adequately and then followed for a period of ten years or more, not one patient developed cervix cancer. Hence, according to the usual estimates (cancer in 4 per cent of gynecological patients, with 89 per cent in cervix), cancer was prevented in more than one hundred of these patients. Karnaky,⁴ reporting statistics from the Jefferson Davis Hospital, found that in the preceding ten-year period there were over 5,000 conizations. In the same period there were 709 cervical cancers. Not one cancer developed in a conized cervix.

In doing hysterectomies, the cervix should be removed. If there is some contraindication to complete hysterectomy, the cervix should be coned.

In connection with chronic irritation, it is important to mention another area in which the persistence of certain forms of irritation is closely related to subsequent cancer. That area is the external genitals, and one such form of chronic irritation is leucoplakic vulvitis. The skin becomes atrophic and white, and there is persistent itching and irritation from scratching, which distinguishes it from simple symptomless leucoderma. Taussig's investigations and accurate recording and analysis of extensive clinical experience with leucoplakic vulvitis established it as one of the important diseases of the external genitals. It causes marked distress at various stages of progress; effective treatment usually requires an extensive and particular plastic operation, and, if allowed to persist, it is very likely to eventuate in cancer.

In Taussig's⁵ series of 155 cases of vulvar cancer, he found that in almost half of them the cancer was preceded by leucoplakic vulvitis. In regard to prevention of cancer, he states: "I am convinced that we have been very

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Original Communications

ADVANCES IN PRACTICAL PREVENTION OF GYNECOLOGIC CANCER*

ROBERT J. CROSSEN, M.D., ST. LOUIS, MO.

THE treatment of cancer is being constantly improved, but the prevention of cancer constitutes the greater lifesaving measure and a most stimulating pioneer field. Cancer prevention is no longer in the theoretical, hazy, wishful-thinking stage. It is here in practical application in day-to-day work. This applies to cancer of the ovary and of the uterus and of the external genitals. As the gynecologist goes about his work he is able to take measures to prevent cancer, instead of waiting till its development jeopardizes the patient's life in spite of the use of the most radical treatment. The development of this preventive work has not been an easy task, but it is here now in effective application. Furthermore, this is a method of lifesaving in which the general practitioner can participate in his daily work, and in which he must take a prominent part, and attain corresponding credit for effective service to his patients.

The prevention of carcinoma in the structures mentioned is made possible by the recognition of two common conditions as predisposing factors, namely, chronic irritation and involution changes. There are many things about the origin of cancer which are still unknown, in spite of the investigations going on in institutions all over the world. But the predisposing influence of chronic irritation and of the involution process are well-established facts which have been known a long time. The advances in cancer prevention which I wish to emphasize have come through the application of this long-known knowledge to the actual handling of patients. The presentation may be divided into two parts—the removal of chronic irritation and the removal of involuting organs.

Removal of Chronic Irritation

In recent years much excellent work has been done by physicians and organizations in promoting one phase of the cancer-prevention problem. In

*Presented, by invitation, at the Seventieth Anniversary Celebration of the Cincinnati Obstetrical and Gynecological Society, Dec. 6, 1946.

weeks was there enough disturbance to make her feel that perhaps an examination was advisable. Some examples from my experience will serve to illustrate the point.

Report of Cases

"Mrs. S., aged 56, had a gradual loss of weight for two years but no local symptoms till a few months before consulting a physician, and even then there was only indefinite discomfort in the abdomen and back. Abdominal examination showed a mass in the left side projecting up from the pelvis, and the patient was sent for operation. The operation revealed an extensive carcinoma of the ovary, which had already invaded irremovable structures. The main tumor was removed and roentgen therapy was given for the extensions. Repeated roentgen treatments prolonged life in fair comfort for a year.

"Mrs. H., aged 52, had come under my care at the age of 47 for treatment of a retrodisplaced myomatous uterus with some prolapse and menstrual irregularity and hot flushes. At that time she was put on conservative treatment and directed to return in two months. She did not return for five years because as she stated, 'There was no special disturbance, and I felt well right along until some months ago.' The principal symptom when the patient came at the age of 52 was enlargement of the abdomen. She thought this had come on gradually, but in the last two weeks it had become well defined and was accompanied with discomfort and an occasional pain. Examination showed pronounced ascites with some masses in the pelvis. Operation revealed general abdominal carcinosis of ovarian origin. No structure could be removed except a specimen for microscopic diagnosis.

"Mrs. P., aged 47, had noticed enlargement of the abdomen for two months, with a feeling of pressure, soreness and frequency of urination for six weeks. Examination showed a pelvic mass extending halfway to the umbilicus. At operation I found a carcinoma of the right ovary with extension to the uterus and other ovary and tube and also to the adherent appendix and abdominal wall. The main mass was removed along with the uterus, the other ovary and tube, the appendix and a specimen from the involved abdominal wall. In each of the structures mentioned, including the abdominal wall specimen, the extension of carcinoma was confirmed by microscopic examination. Postoperative roentgen therapy was employed, with unexpectedly good results. The operation was in 1933, and the patient is still well and strong and without evidence of recurrence. The patient was a physician's wife. Her sister had died of ovarian carcinoma and her mother of cancer of the stomach. In spite of these facts favoring close observation, the growth of the ovarian cancer was so 'silent' that it had extended into surrounding structures before there was any intimation of its presence.

"Miss R., aged 48 years, was a patient for whom, at the age of 43, I had performed a hysterectomy for myoma with right salpingo-oophorectomy and appendectomy, and recovery was without special incident. Five years later she was sent by her physician for treatment of a pelvic tumor extending almost to the umbilicus. She had noticed some pressure in the abdomen for about a year but gave little thought to it. An increase in the pressure discomfort finally caused her to go to her physician, who found the tumor. Operation showed extensive abdominal carcinosis originating in the left ovary. No structure could be removed. Repeated roentgen treatments kept the patient in fair comfort for nearly a year.

"The lesson of this case is that I should not have left an ovary at age 43. I thought then that it was advisable, but I know better now.

"Mrs. G., aged 55 years, went to her physician because she had noticed discomfort in the left side of the lower part of the abdomen off and on for a month or two. Examination showed a tumor the size of a fist filling the left side and central portion of the pelvis. Operation revealed a carcinoma of the left ovary. It had already spread to adjacent organs and into irremovable structures. The main mass was removed, and with roentgen therapy the patient lived for a year and eight months."

remiss in our preventive measures in the past. The incidence of vulvar cancer might very possibly be cut in half if we would adopt complete vulvectomy in cases of well-developed leucoplakic vulvitis, and give critical attention to vulvar warts and urethral caruncles and other chronic irritative lesions. Particularly, in leucoplakic vulvitis would I stress the advantages of surgery over nerve resection or treatment with ovarian hormones. The latter undeniably often decreases the pruritus, but the question whether the use of such carcinogenic substances may not at least predispose to the development of a cancer might very well be raised."

Removal of Involuting Organs

Another fact which has long been known is that the involution process favors cancer development. That is why carcinoma occurs so much more frequently in persons past middle life. It is only recently, however, that this well-established fact is being practically applied to cancer prevention.

As there is no way to stop the aging process, and as aging persons wish to live out their span of life, there did not seem much chance to use the knowledge stated in cancer prevention. However, there are two organs which go through involution shortly after middle life, namely, the uterus and the ovary. They are temporary organs, their functioning being limited to the childbearing period. After the menopause they are no longer functioning organs, but involuting structures on their way out of the active economy. They touch no vital interest of the individual—their special task of childbearing with its associated hormone production has been performed and finished. They are not only functionless, but they carry the special menace of involuting structures, which is a predisposition to cancer development.

Involuting Ovaries.—The most serious menace comes from cancer of the involuting ovary. Though less frequent than cancer of the uterine endometrium, the usual symptomless progress to incurability of ovarian cancer causes it to be fatal in a much larger proportion of the cases.

Primary ovarian carcinoma is the most insidious of the pelvic malignancies, and the one most frequently overlooked until it has reached a hopeless stage. It causes so little disturbance that most patients do not realize there is anything wrong until the malignant infiltration has advanced beyond cure. Attention was called to this striking phenomenon by H. S. Crossen⁶ and the menace is so serious and the recognition of the condition so important to all physicians that considerable space is taken here to bring out the details by the following quotations from the article:

"By 'silent' I mean without symptoms—without any indication to the patient that a serious process is present. Patient after patient is seen with an extensive growth of long duration but with only a short period of local symptoms. The first visit to the physician shows a large growth or ascitic fluid from peritoneal carcinosis. The advancing carcinoma causes only such minor disturbances that the patient hardly notices them. Thinking back, when questioned, she recalls that the abdomen has been a little larger for a year or so or that there was bloating or some frequency of urination, but only in the last few

Radiation treatment is, of course, contraindicated in the childbearing period, and also in those cases in which the myoma is causing trouble that would not be relieved simply by cessation of ordinary myoma activity. On the other hand, there are many myoma patients in the age of involution, whose bleeding and other troublesome symptoms can be entirely relieved simply by curettage to exclude to malignancy, conization when cervicitis is present, and radium treatment to stop myoma activity. This takes care of the immediate disturbance without the serious risk of hysterectomy, but it does not remove the involuting uterus and ovaries with their risk of future malignancy.

How do these two risks compare? What weight should be given to each, in advising the patient? In order to answer these important questions, we must know (a) the risk of hysterectomy with double oophorectomy, and (b) the risk of future malignancy in these involuting organs, without radiation and with radiation. From general operative statistics we know the average mortality risk in removal of the uterus and ovaries for myoma or other nonmalignant condition. With an experienced operator it may be reckoned at 1 to 2 per cent, depending on the condition of the patient. In order to obtain definite information as to the future-malignancy risk in myoma patients treated by radiation, as well as to obtain definite information on many other items, we made an analysis of our series of 549 myoma patients selected for myoma radiation, and recently reported the results.⁷ The plan of procedure included curettage to exclude malignancy, conization when there was cervicitis, and an intrauterine radium treatment. Incidentally, it may be mentioned that the primary curettage revealed a complicating endometrial carcinoma in 23 of these 549 patients who appeared to have only a simple fibroid.

In regard to malignancy development in patients with myoma, in our series of 2,662 myoma patients 526 were treated by radiation, and the malignancy developments in the two groups are shown in the following table.

| | | |
|-----------------------|------------------------------------|------------|
| Cancer of Endometrium | } In 2136 nonradiated myoma cases. | 37 (1.7%) |
| | } In 536 radiated myoma cases. | 4 (0.7%) |
| Cancer of Ovary | } In 2136 nonradiated myoma cases. | 13 (0.68%) |
| | } In 536 radiated myoma cases. | 1 (0.19%) |

Each type of malignancy was more than twice as frequent in the non-radiated cases as in the radiated.

Here we have dependable data as to the future malignancy risks in myoma patients with involuting organs. Without radium treatment, the malignancy risk for uterus and ovaries is 2.38 per cent. With radium treatment, the risk is 0.89 per cent. Thus the radiation procedure which we employed not only took care of the immediate trouble in most cases, but also cut to one-third the risk of future malignancy. However, it did not eliminate that risk—as operative removal would have done, but at a decided immediate mortality risk.

Decision as to what is safest and best for each patient requires a careful assessment for that individual of the three important factors—the chance of satisfactory relief by the radiation procedure, the risk of later malignant devel-

And so on, with depressing regularity, down the series of twelve cases the victim notices some bloating and enlargement of the abdomen, comes for examination which shows ascitic fluid with a pelvic mass, and operation reveals an extensive irremovable ovarian carcinoma. Continuing to quote:

"These 12 cases show the symptomless progress to extensive involvement which represents the natural history of ovarian carcinoma. Some patients are fortunate enough to have some coincident disease which takes them to a physician, who, in the course of routine pelvic examination, discovers the silent growth before it has progressed beyond removal. Occasionally some early complication of the growth causes pain which leads to examination and discovery of the cancer in a curable stage. The favorable cases of ovarian cancer are discovered thus through routine examination or accidental complication. These fortunate exceptions must not be allowed to divert attention from the symptomless onset and symptomless progress of uncomplicated ovarian cancer. It is ordinarily a slow-growing infiltration which penetrates into irremovable structures before the appearance of warning symptoms.

"The aggregate of deaths from this cause is large, much larger than is generally appreciated. To the known cases must be added the unrecognized ones, with death certificate designations of 'ascites' and 'abdominal cancer.' A large proportion of the cases of general abdominal carcinosis originate in an ovary.

"The silent character of the onset and progress of ovarian cancer seals the doom of these individuals, unless measures which are really effective against the serious difficulties of the situation are put into practice. The following three steps are advisable and urgent in reducing deaths from this insidious disease:

"1. Removal of the involuting ovaries whenever the abdomen is opened under circumstances which permit of such removal.

"2. Insistence on regular periodic pelvic examinations. These periodic examinations for silent ovarian carcinoma should be made every six months, instead of the once yearly which was formerly supposed to provide adequate safety. Also, one must give the time and thought necessary to make this advice of real benefit to each patient, instead of simply throwing out some general remark to act as a salve to conscience should the patient return later with incurable cancer.

"3. Utilization of every opportunity afforded by anesthesia for a minor vaginal operation, to make deep accurate palpation of the ovarian areas, the findings to be recorded in the operative note for future reference and comparison."

Involuting Uterus.—Since our study of the cancer menace in involuting ovaries and the advisability of their removal in suitable cases whenever the abdomen is opened in the age of involution, we have given much thought to the problem of choice between radical and conservative treatment of nonmalignant uterine lesions which are giving the patient so much trouble that serious treatment is required. This problem is encountered when handling patients with uterine myoma causing troublesome symptoms which persist in spite of palliative measures. Of course, some myomas cause no symptoms and require no treatment, while in other cases the troublesome symptoms may be sufficiently relieved by minor measures. But persisting serious symptoms confront us with the problem of choosing between operative removal of the fibroid and stopping its activity by radiation.

It may be well to add here a word of warning concerning the use of estrogenic hormones in the menopause, and particularly in patients with delayed menopause. Bleeding beyond the usual age calls, not for estrogenic medication but for investigation to determine if endometrial carcinoma has already begun. In view of evidence presented, it would seem unwise to use large doses or prolonged dosage of estrogenic substances in patients in the menopause age. If there are troublesome symptoms, Engle has shown that most of the menopausal symptoms can be controlled by small doses of thyroid plus phenobarbital. If in spite of this, hot flushes continue to a troublesome extent, stilbestrol may be added, but in minimum doses required to give relief.

Résumé

1. Cancer prevention involves the removal of chronic irritation, by conization for cervicitis and by vulvectomy for leucoplakic vulvitis, and the removal of involution ovaries and uterus under suitable circumstances.

2. Periodic examinations are necessary to discover chronic irritation before malignant development starts and to discover cancer in involuting ovaries or uterus or breasts while it is still in a curable stage.

Yearly checkups were formerly considered sufficient, but owing to the difficulties of detecting early ovarian cancer that interval is too long to guard the patient against advanced malignancy. That fact was learned by bitter experience. A patient whose adnexal areas were apparently clear on examination returned seven months later with an irremovable ovarian cancer. Careful checkups at six-month intervals for the two decades, aged 40 to 60 years, constitute the minimum requirement for reasonable safety from incurable malignancy.

3. In addition to the usual deep pelvic palpation and the speculum examination and the check of the breasts for beginning infiltration, the checkup should include percussion of the flanks for possible ascitic fluid. A small amount of free fluid in the peritoneal cavity is often the first demonstrable sign of the chronic peritoneal irritation associated with ovarian carcinomatous infiltration.

4. Owing to the cancer-potential of the involuting ovaries and the "silent" advance to incurability of most ovarian cancers, it is advisable to remove the involuting ovaries whenever the abdomen is opened in the climacteric age (43 years and later), except where there is some definite contraindication to this additional work.

5. The cancer-potential of the involuting endometrium should be taken into consideration when handling nonmalignant uterine conditions requiring serious treatment. For example, a myoma causing persistent serious symptoms in spite of palliative measures confronts us with the alternative of stopping the myoma activity by radium treatment (with curettage to exclude malignancy and conization if cervicitis is present) or removing the growth by the major operation of hysterectomy.

opment, and the risk of a major operation. The wish of the patient is another factor which has some bearing on the decision. Some patients would decidedly prefer the myoma-radiation program, with its minor immediate risk and subsequent oversight, rather than the major operation with its greater immediate risk and greater future security.

Our conclusions as to the place of radium treatment in the handling of climacteric patients with troublesome myoma, keeping in mind the cancer potential in the involuting ovaries and uterus, are as follows:

1. It is effective in stopping myoma activity and associated troublesome symptoms in 90 per cent of properly selected cases.
2. It reduces to one-third the risk of future malignancy. But it still leaves a risk of 0.89 per cent, which definite risk must be given due weight in deciding between radium treatment and operative removal, in the individual patient with her special local and general conditions.
3. When the patient is a good operative risk and has first-class operative facilities available, removal of the complete uterus and the involuting ovaries would seem the safer plan.
4. For the handicapped patient with high operative risk, the myoma-radiation plan here described is a lifesaving measure and strongly indicated, where the serious symptoms are of a type to be relieved by it.

A word about delayed menopause as an indicator of increased susceptibility to malignancy. Delayed menopause (prolongation of periodic flows up to ages 48, 50, and 52 years, and older) does not signify "renewal of youth," as some women suppose. It signifies persisting ovarian stimulation keeping up uterine congestion and erratic activity in involuting organs, which means an increased cancer potential in the endometrium of that individual.

In 1935, Dr. Hobbs and I analyzed a series of fundal carcinoma cases to determine whether delayed menopause, with its prolonged estrogenic activity, was more common in endometrial, carcinoma cases than it was in normal cases. We found that in 60 per cent of the carcinoma cases the patients had menstruated to the age of 50 years in contrast with only 15 per cent in the normal cases. In a recent article, Randall calls attention to the frequent association of delayed menopause and corpus cancer. He also found that delayed menopause was four times more frequent in malignant cases than in the nonmalignant ones.

In summarizing, then, we can say that, though the specific cause of endometrial carcinoma is not yet known, circumstantial evidence points to the prolonged action of endogenous estrogen beyond the normal menopause age as an important factor. Hence the importance of eliminating this abnormal influence, for the longer it continues the greater the likelihood of carcinomatous development in the involuting endometrium. This sinister influence can be easily eliminated by radium treatment, which stops the erratic ovarian activity. Curettage along with the radium treatment determined whether or not malignant change has already begun.

A STUDY OF THE CAUSES OF FETAL AND NEONATAL MORTALITY ON THE OBSTETRIC SERVICE OF BELLEVUE HOSPITAL

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FETAL and neonatal mortality rates are directly proportionate to progress made in maternal and infant care. We cannot remain satisfied with our maternal and infant care programs until we have made definite strides toward an appreciable reduction in these mortalities. While a definite reduction in the maternal mortality rate of the U. S. has been recorded in the past decade, the reduction in the fetal and neonatal mortality has not been proportionate.

In 1945, there occurred 105,000 fetal and neonatal deaths, the latter category accounting for 10.4 per cent of the total deaths in the U. S. in the first month of life⁹ from all causes. The high mortality rate compares closely to the rates accorded to the major causes of death among our general population. It is as important to reduce the number of deaths among newborn infants as it is to reduce the death rate from cancer, heart disease, or tuberculosis.

In New York City, the stillbirth and neonatal (first month of life) mortality rate for 1944 was 31.2 per 1,000 live births, as compared with 57.2 per 1,000 live births in 1930. The rate of reduction of fetal and neonatal mortality in the United States has been progressive, but slow. The infant mortality rate for 1945 in the United States according to recent estimates of the Bureau of Census is the lowest on record, 38.1 per 1,000 live births. The corresponding rate for 1944 was 39.2. Despite this decrease, concern has been voiced over the relatively high fetal and neonatal death rates.^{5, 10, 11}

In order to effect an adequate reduction in the fetal and neonatal mortality rate, it is important to obtain accurate information concerning the causes of death in stillbirths, and in newborn infants. Efforts then can be directed toward the control of the major factors influencing these results. This object we can obtain best through careful autopsy examinations correlated with the clinical facts related to this fatality. The causes of death as ascertained from death certificates are too vague and misleading, since most are not supported by postmortem examination. Such a study of fetal and neonatal mortality can best be carried out on a large obstetric service. This presentation is an attempt to analyze the causes of such deaths on the obstetric service of Bellevue Hospital.

During the ten years beginning on July 1, 1933, and ending May 31, 1943, 16,669 deliveries took place in Bellevue Hospital. During this period, there were 1,114 fetal and neonatal deaths. The uncorrected mortality rate was 6.6 per cent. After excluding 312 nonviable infants, the corrected fetal death rate was 4.8 per cent. The death rate among term infants during this period was

This calls for careful consideration of three factors, namely, (a) the chance in that particular case of securing relief by the radiation program, (b) the future risk of malignant development in uterus or ovaries, and (c) the immediate risk of hysterectomy and double oophorectomy. In our report of five hundred myoma-radiation cases, previously referred to, may be found tabulated the cases given permanent relief and those not relieved. Also, we found that though the risk of future malignant development was cut to one-third by radium treatment, there still remained a malignancy risk of 0.89 per cent. The mortality risk of hysterectomy and double oophorectomy may be reckoned at 1 to 2 per cent, depending on the condition of the patient and the skill of the operator. Giving proper weight to these various factors in your study of the individual case will insure the safest and best treatment to your patient.

In general, for the good operative risk, the seriously troublesome myoma occurring in the age of involution is preferably handled by complete hysterectomy and double oophorectomy. On the other hand, for the seriously handicapped patient the radium plan in a suitable case is a lifesaving measure, in that it stops the serious myoma activity without the great risk of a major operation.

6. Leucoplakic vulvitis eventuates in cancer in a considerable proportion of the cases. In Taussig's series of 155 vulvar cancers, nearly half were preceded by leucoplakic vulvitis. Hence, the importance of prompt vulvectomy for this condition, unless there is a good response to vitamin A therapy as suggested by Hyams and Bloom.⁸

7. Delayed menopause indicates erratic endometrial and ovarian activity which increases the susceptibility to malignant development. It should be stopped by radium treatment, with associated curettage to exclude endometrial malignancy, conization if cervicitis is present, and accurate palpation of the ovarian areas under the anesthesia, with recording of findings for future reference and comparison.

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was higher (43.6 per cent), while one-third of the viable premature infants failed to survive for similar reasons (Table III). Other statistical studies of fetal mortality have consistently reported prematurity as the most frequent cause of death.^{5, 8, 11, 14}

TABLE III. CAUSE OF DEATH IN 319 VIABLE PREMATURE BABIES

| | LUNG LESIONS | | PER CENT OF TOTAL DEATHS |
|---|--------------|----------|-----------------------------|
| | NUMBER | PER CENT | |
| A. Prematurity | 105 | | 32.90 |
| B. Pulmonary lesions | 68 | | 21.30 |
| 1. Massive aspiration of amniotic fluid | 35 | 51.5 | 10.97 |
| 2. Pneumonia | 25 | 36.7 | 7.80 |
| a. Congenital | 1 (4%) | | |
| b. Aspiration | 20 (80%) | | |
| c. Bacterial—origin undetermined | 4 (16%) | | |
| 3. Hemorrhage | 4 | 5.9 | 1.25 |
| 4. Hyaline membrane | 4 | 5.9 | 1.25 |
| C. Birth trauma | 41 | | 12.80 |
| D. Maceration | 50 | | 15.60 |
| E. Congenital anomalies | 21 | | 6.50 |
| F. Syphilis | 20 | | 6.20 |
| G. Sepsis | 7 | | 2.20 |
| H. Erythroblastosis | 2 | | 0.62 |
| Probable erythroblastosis | 5 | | 1.56 |
| I. Other causes—Malnutrition | 1 | | 0.30 |

This group represents a large number of infants to die from a single cause. At postmortem examination the only findings were those attributable to immature development of the vital organs of the body. The lungs have failed to develop sufficiently to allow for ready and adequate transmission of oxygen to support life. The immaturity of the lungs explains the persistent cyanosis after birth in spite of continuous oxygen administration.

The kidneys in the premature are not completely developed, and the absence of a full complement of well-formed glomeruli and tubules impedes the normal functioning power of these organs. In the fetus, glomerular development continues until about the thirty-fourth or thirty-sixth week of intra-uterine life.

The mucosa of the gastrointestinal tract has not attained its full capacity of assimilation of food. The digestive glands are smaller and fewer in number. Careful attention in providing these infants with easily assimilable food in small quantities and at frequent intervals is essential to their survival, and requires expert supervision.

The temperature-regulating mechanism in the premature infant is extremely unstable. Attention is necessary to avoid excessive loss of body heat and to provide an environment which will maintain a normal body temperature. Because of the reduced or complete lack of immunity, these infants are subject to infections, and rigid precautions must be observed in order to prevent their occurrence.

In order to reduce the mortality rate from prematurity, it appears obvious that careful and intelligent attention must be given in the care of the premature after delivery. The best environment for these infants must be supplied under adequate supervision by specially trained personnel.^{10, 10} Their care presents four major problems:

1. Maintenance of body temperature.
2. Prevention of cyanotic attacks.
3. Proper nutrition.
4. Prevention of infection.

1.97 per cent, while the mortality rate among viable premature infants was 35.2 per cent (Tables I and II). Eight hundred sixty-eight or 77.9 per cent of the stillbirths or infants dying in the neonatal period were examined post mortem by the obstetric pathologist. Complete autopsies were performed on 318 term, 319 viable premature, and 231 nonviable premature infants.

Results.—The four major causes of fetal and neonatal deaths as determined from this study was found to be (1) prematurity; (2) pulmonary lesions; (3) birth trauma; and (4) maceration, following antepartum or intrapartum fetal deaths, often of unknown cause (Fig. 1).

I. Prematurity.—This was found to be the greatest single cause of death (Fig. 1). In 27.6 per cent of all the autopsies it was felt that death occurred because the vital organs were insufficiently developed to carry on with the proper functioning necessary to maintain life. Considering the premature group of infants alone (viable and nonviable), the death rate from this cause

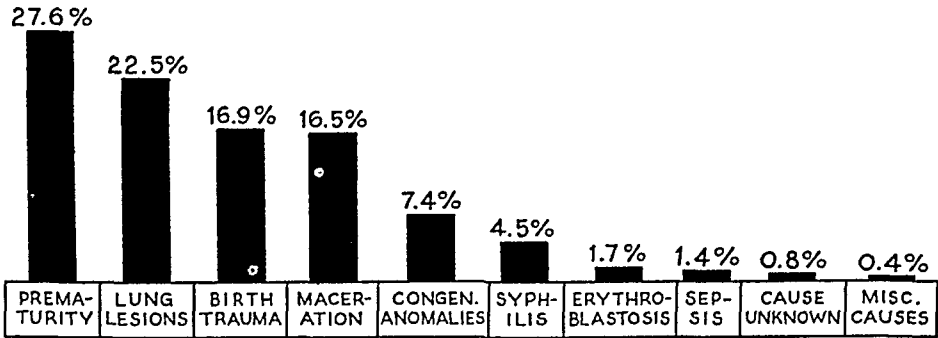


Fig. 1.—Causes of fetal and neonatal deaths, 868 autopsies.

TABLE I. FETAL DEATH RATE DURING A TEN-YEAR PERIOD BEGINNING JULY 1, 1933, AND ENDING MAY 31, 1943

| | | |
|---|--------|-------|
| Total Deliveries | 16,669 | |
| Total fetal and neonatal deaths | 1,114 | |
| Uncorrected fetal mortality | | 6.6% |
| Nonviable deaths | 312 | |
| Corrected fetal mortality | | 4.8% |
| (This figure includes macerated stillbirths and babies dying of congenital anomalies) | | |
| Total autopsies performed | 868 | |
| Autopsy percentage rate | | 77.9% |

TABLE II. CORRECTED DEATH RATE OF TERM AND PREMATURE INFANTS

| YEAR | TERM DEATH RATE | PREMATURE DEATH RATE |
|---------------------------|-----------------|----------------------|
| June 1, 1934—May 31, 1935 | 92 (6.10%) | 43 (63.2%) |
| June 1, 1935—May 31, 1936 | 48 (3.00%) | 40 (49.3%) |
| June 1, 1936—May 31, 1937 | 34 (2.80%) | 24 (39.3%) |
| June 1, 1937—May 31, 1938 | 21 (1.50%) | 26 (44.0%) |
| June 1, 1938—May 31, 1939 | 9 (0.65%) | 56 (35.8%) |
| June 1, 1939—May 31, 1940 | 11 (0.84%) | 34 (15.5%) |
| June 1, 1940—May 31, 1941 | 12 (0.90%) | 51 (40.5%) |
| June 1, 1941—May 31, 1942 | 12 (0.74%) | 18 (12.2%) |
| June 1, 1942—May 31, 1943 | 18 (1.20%) | 32 (17.3%) |
| Average death rate | 1.97% | 35.2% |

Note: The above figures include macerated stillbirths and babies dying of congenital anomalies. The premature deaths exclude nonviable infants living a few hours.

or in the neonatal period. Pulmonary lesions were found most frequently as a cause of death (21.3 per cent). The most frequent type of lung lesions encountered were massive aspiration of amniotic fluid and pneumonia. Hemorrhage and hyaline membrane of the lungs occurred in a smaller number of cases. The other major causes of death in this group is shown in Table III.

Death from pneumonia was found to be a great hazard of the neonatal period. Seven and eight-tenths per cent of the viable premature infants died of pneumonia contracted during the first month of life. Aspiration pneumonia resulting from the inhalation of foodstuff was the greatest single hazard. Eighty per cent of the pneumonia in the premature was of this type. That this hazard can be greatly reduced during the neonatal period by proper care is attested to by the fact that in Bellevue Hospital, death from this type of pneumonia has decreased markedly in recent years. Twenty premature infants died of aspiration pneumonia and 16 of these deaths occurred during the first three years of this ten-year period. In a similar manner, the number of cases of premature babies dying of sepsis has been reduced. The seven deaths from sepsis among the viable premature infants occurred during the first three years of this study. This reduction undoubtedly has been brought about by the strict observation of precautions by a trained personnel.

II. *Pulmonary Lesions*.—The second most frequent condition accounting for death was found in the lungs (22.5 per cent). (Fig. 1.) Among the group of term infants, these lesions constituted the commonest single cause of death found (39.3 per cent). (Table IV.) In the viable premature group 21.3 per

TABLE IV. CAUSE OF DEATH IN 318 TERM BABIES

| | LUNG LESIONS | | PER CENT OF TOTAL DEATHS |
|--|--------------|----------|-----------------------------|
| | NUMBER | PER CENT | |
| A. Pulmonary lesions | 125 | | 39.30 |
| 1. Massive aspiration of amniotic fluid | 83 | 66.4 | 26.00 |
| 2. Pneumonia | 26 | 20.8 | 8.17 |
| a. Congenital | 12 (46%) | | |
| b. Aspiration | 7 (27%) | | |
| c. Bacterial—origin undetermined | 7 (27%) | | |
| 3. Hemorrhage | 15 | 12.0 | 4.70 |
| 4. Congenital cystic lung | 1 | 0.8 | 0.30 |
| B. Birth trauma | 76 | | 23.90 |
| C. Maceration | 56 | | 17.60 |
| D. Congenital anomalies | 32 | | 10.06 |
| E. Syphilis | 4 | | 1.20 |
| F. Sepsis | 5 | | 1.57 |
| G. Erythroblastosis | 6 | | 1.88 |
| Probable erythroblastosis | 2 | | 0.63 |
| | | | 2.51 |
| H. Cause unknown | 8 | | 2.50 |
| I. Other causes—Cerebrospinal meningitis | 2 | | 0.63 |
| Epidermolysis bullosa | 1 | | 0.31 |

cent were found to have lung lesions of serious proportion. These findings are in agreement with the observations of others that the majority of fetal and neonatal deaths are respiratory in their clinical picture.⁷

Aspiration of amniotic fluid: in massive amounts was the type of lung lesion most frequently demonstrable at autopsy (60.2 per cent). (Fig. 2.) In the group of term babies this lesion accounted for 26 per cent of the total deaths, while in the viable premature group only 10.97 per cent showed this condition. The higher incidence of aspiration of amniotic fluid in the term baby is probably related to the greater incidence of fetal asphyxia accompanying longer and more difficult deliveries.

From the above observations, obstetricians might be tempted to absolve themselves of all responsibility in handling premature infants and to throw the burden entirely upon the shoulders of the pediatricians. However, the obstetrician plays a vital role in the initial handling of these cases, and it is his responsibility to turn over the premature to the pediatrician in the best condition possible. Of paramount importance is the part that the obstetrician must play in the management of the pregnancy, labor, and delivery, and in the initiation of respirations immediately after birth.¹⁸

To effect a lowering of the death rate from prematurity in this group the obstetrician must attempt to delay the onset of labor as long as possible. Certainly no procedure should be instituted for the induction of labor without sufficient indications until a period in development has been reached which will give the fetus the best opportunity for survival after birth. Whenever feasible, maternal complications of the prenatal period, which are associated with a high incidence of premature births,⁸ should be treated conservatively as long as the delay does not create a serious hazard to the mother.

The premature infant is susceptible to injury by the normal processes of labor tolerated without harm by the term fetus. Too frequent or too strong uterine contractions during labor may produce intracranial injury (cerebral or arachnoid hemorrhage). Scott¹⁵ observed that the highest death rate in prematures occurred following a short labor with frequent strong contractions of the uterus, with consequent injury to the fetus. Excessive use of sedation must be avoided because of the depressive effect on the respiratory center.^{12, 15} The use of oxytocics during labor should be condemned for very obvious reasons. Premature rupture of the membranes is associated with a higher mortality in the premature infant.¹⁵ Artificial rupture of the fetal membranes is contraindicated in order to avoid direct pressure on the immaturely developed fetal skull.

The second stage of labor should be shortened. The strain on the fetal head by the pressure of a resistant pelvic floor should be eliminated by performing an episiotomy, and the delivery may be completed with low forceps.^{8, 16} Twenty-five and eight-tenths per cent of the prematures (viable and nonviable) in this study, sustained birth trauma. An appreciable reduction in deaths from intracranial injury in these infants has been attained at Bellevue Hospital by applying such measures in the second stage with a view to reducing the forces to which the prematures are subjected at this time.¹⁶ Other investigators have shown that the lowest mortality rate occurred in the group of premature infants delivered by forceps, the highest death rate in deliveries by version and breech extractions, and the second highest rate in spontaneous deliveries.¹⁵

Immediately after delivery, energetic measures must be taken to initiate respirations. The most important of these measures is adequate aspiration to ensure an unobstructed flow of air to the lungs.¹ This is particularly important if some fetal asphyxia occurred in utero resulting in the aspiration of amniotic fluid. Eleven per cent of the viable premature infants were found to have massive aspiration of amniotic fluid at autopsy. This degree of aspiration of amniotic fluid may be avoided, in many instances, by prompt delivery of the fetus when fetal distress is observed during the terminal stage of labor.

Since prematurity alone is the greatest cause of fetal and neonatal mortality, it appears obvious that any marked reduction in the gross neonatal mortality must be brought about by a reduction in premature births, or by reducing the number of deaths from prematurity.

Although prematurity alone accounted for 32.9 per cent of the deaths among viable infants, autopsy findings indicate that two-thirds of these infants showed additional pathologic conditions which developed either in utero

quently exhibit evidence of respiratory distress with labored, grunting respiration, dilatation of the alae nasi, and marked retraction of the costal margins. The cry is feeble, and varying degrees of cyanosis is present. Some of these clinical features may result from direct injury to the respiratory center by the asphyxia. The delay in establishing regular respiratory activity probably is due to injury to the center of respiration. However, the other clinical features may be explained by the direct effect on the functioning capacity of the lungs from massive or moderate aspiration of amniotic fluid.

The various causes of fetal asphyxia and the relative merits of the use of the terms anoxia, apnea, and asphyxia have been discussed by others.^{1, 3, 6, 7, 13} Whatever the cause of the fetal asphyxia, the respiratory center is susceptible to the chemical changes produced by anoxia.¹⁹ In the production of experimental anoxia, Eastman and Kreiselman⁷ noted that the effect of mild degrees of anoxia was to increase the respiratory and cardiac heart rates. They explain this as a compensatory mechanism designed to supply the tissues with an adequate oxygen supply. This may explain the initial increase in the fetal heart rate above normal which occurs in early phases of fetal asphyxia. As the anoxic state continues, a stage of "oxygen crisis" is reached and the compensatory mechanism fails to supply sufficient amounts of oxygen to the tissues. Respirations stop and, following this, the heart rate is greatly slowed. Some such mechanism must occur in fetal asphyxia. The initial effect of respiratory stimulation caused by the anoxic state produces an increase in the rate and depth of intrauterine fetal respiratory movements^{2, 17} causing the infant to aspirate large quantities of amniotic fluid. If the anoxic state continues, fetal intrauterine death occurs from irreversible damage to the central nervous system. Yant²⁰ has demonstrated that asphyxia results in congestion, perivascular edema, and hemorrhage into nerve tissue resulting in destruction of the neuron. Examination of the lungs in these infants will show evidence of extensive aspiration of amniotic fluid.

If intrauterine fetal death does not result from the anoxia, the aspiration of large quantities of amniotic fluid which occurred in utero as the result of the anoxic state will in itself prolong or aggravate a state of anoxia after birth. The alveolar sacs, distended by the aspirated fluid, are responsible for the clinical evidence of respiratory distress as previously described. In these cases, the massive aspiration of amniotic fluid is a major cause of death in that it causes a prolonged and fatal state of asphyxia similar to death caused by drowning.

The chance for survival of these infants is directly proportionate to the duration of the anoxic state, to the amount of amniotic fluid aspirated, and to the state of lung development. It appears obvious that a premature infant whose alveoli are immature will be more gravely embarrassed by a smaller degree of aspiration of amniotic fluid than a term baby. A fetus showing signs of intrauterine distress should be delivered as soon as conditions, compatible with the safety of the mother, permit. Prolonged fetal distress will not only result in aspiration of larger quantities of amniotic fluid, but will increase the danger from irreversible tissue damage to the central nervous system resulting from the anoxia.

Pneumonia: was the second most frequent type of lung lesion encountered at autopsy (27 per cent) (Fig. 2), accounting for 8 per cent of the total deaths in both the premature and the term groups of babies. However, in the term group, 20.8 per cent of the lung lesions were of this type, whereas in the viable premature babies its incidence increased to 36.7 per cent (Tables III and IV). Tyson,¹⁹ in studying fetal mortality in Philadelphia, found that pneumonia was responsible for 5 per cent of the total mortality.

The gross appearance of the lungs does not present any characteristic features suggesting this condition. The lungs appear congested but otherwise normal in appearance, and often retain their capacity for floating when immersed in water. The presence of aspirated amniotic fluid can be detected only on microscopic examination of the lungs.

Normal amniotic fluid has a high cellular content derived from epithelial desquamation of the vernix caseosa of the fetal skin. Meconium droplets are also present. These elements are readily demonstrated in the sediment of a centrifuged specimen of amniotic fluid. When large amounts of amniotic fluid are aspirated into the lungs, these telltale flattened epidermoid cells and meconium droplets will be found in the alveolar spaces in large numbers. The extent of lung involvement depends upon the degree of aspiration. In massive aspiration of amniotic fluid most of the alveolar sacs are filled with the cellular remnants of the amniotic fluid. In cases of a moderate degree of aspiration, areas, very frequently in a lobular pattern, of normal uninvolved alveoli are found.

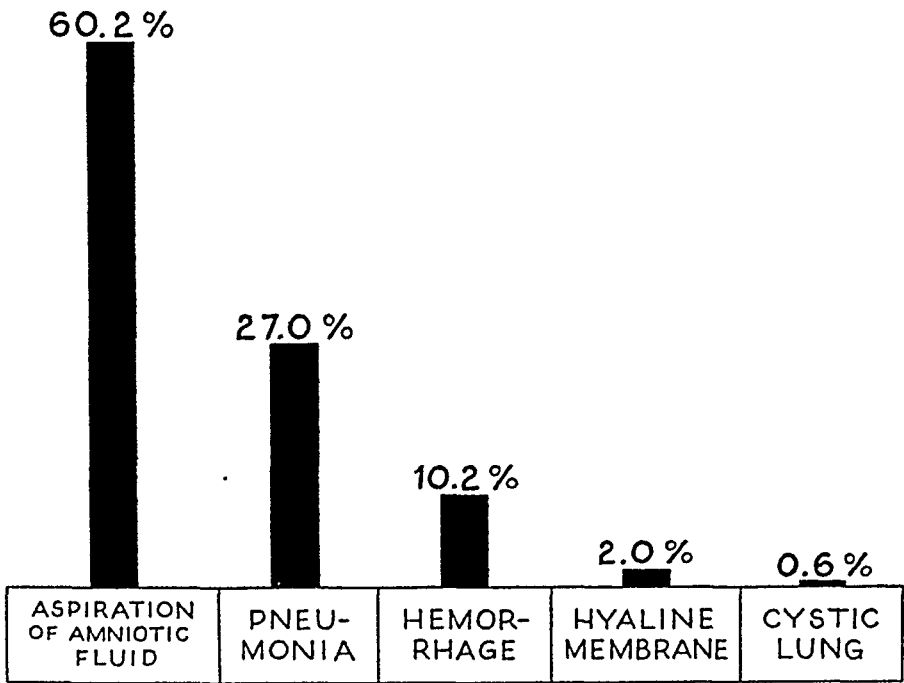


FIG. 2.—Types of lung lesions producing fetal or neonatal death.

A few scattered epidermoid cells frequently can be seen in the alveolae of infants who have died from other causes. These are usually derived from aspiration of amniotic fluid, which normally fills the trachea and upper bronchial passages, with the initiation of the first breath after birth. They cannot be regarded as having any serious significance.

Aspiration of large quantities of amniotic fluid occurs during intrauterine life as a result of an anoxic or asphyxial state in the fetus. Therefore, a discussion of this lesion must necessarily include some discussion of fetal anoxemia. Intrauterine asphyxia is known to produce physiologic and pathologic changes involving every organ and tissue in the body.^{3, 7} The pathologic changes produced in the lungs have been described above. Should these infants survive birth, they present clinical features of respiratory difficulty. They appear extremely pale and flaccid with weak, slow heart action. Respirations are initiated with difficulty and, once established, these infants fre-

infant and were usually related to the performance of a difficult operative delivery. Subarachnoid and subventricular hemorrhages were characteristic of the lesions found in the premature infant. In contrast they were found frequently in babies born spontaneously. In babies of approximately thirty-four to thirty-eight weeks gestation, there frequently occurred combinations of the dural lesions seen in the term baby and the vascular lesions observed in the premature infant.

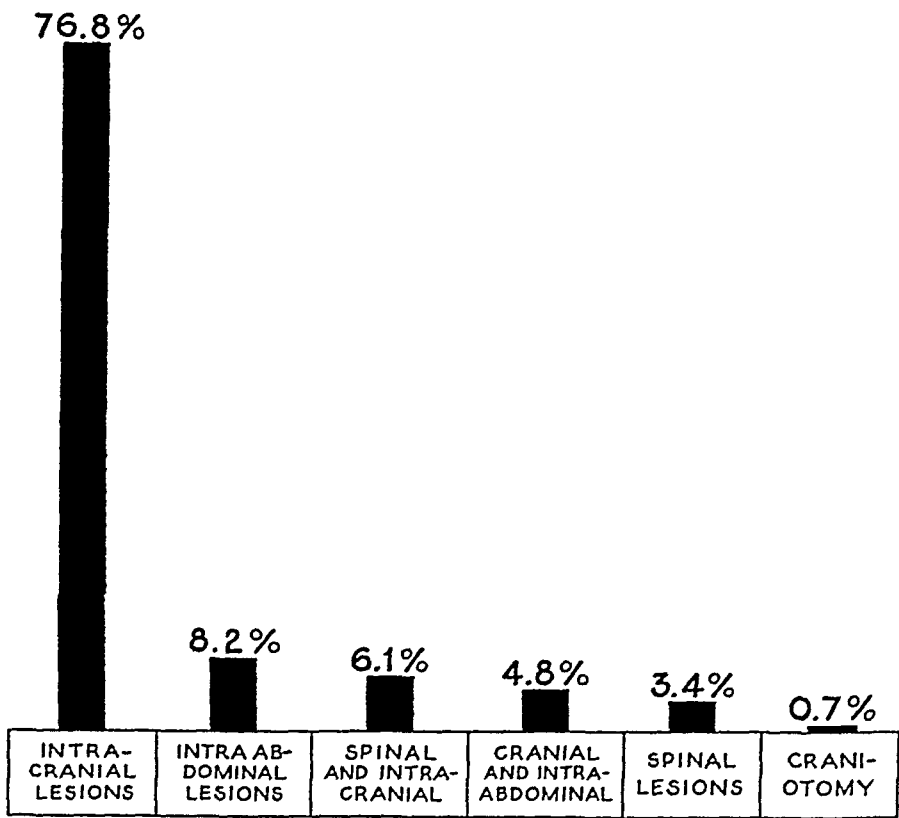


Fig. 3.—Types of birth trauma producing fetal death.

Spinal injuries involved the spinal cord, the vertebral column or both. These were more frequently combined with severe intracranial lesions. Most of the spinal injuries were limited to the cervical region, usually resulting in a fracture dislocation of the cervical vertebra and most frequently involving a separation of the epiphysis from the diaphysis between the sixth and seventh cervical vertebra. Occasionally disarticulation of the atlas and axis occurred. Following disarticulation of the vertebra, direct injury to the spinal cord may occur causing incomplete or complete cord lacerations. These injuries were usually sustained during delivery of the aftercoming head in breech presentations but occasionally during delivery of a large baby with impacted shoulders.

Intra-abdominal injuries were found to involve the liver, adrenals or kidneys and resulted from direct pressure on the abdomen during delivery of the breech or too strenuous force used in resuscitation, particularly in the premature. The types of lesions observed were (1) rupture of the liver; (2) hemo-peritoneum resulting from the rupture of a subcapsular hematoma of the liver; (3) hemorrhage into the adrenal medulla; and (4) hemorrhage into the kidney.

IV. *Maceration: Cause Unknown.*—A large group of the babies (16.5 per cent) autopsied were in a state of extensive maceration. Detailed anatomic dissection or microscopic study was impossible. In these cases, sections of the

For purposes of classification, the types of pneumonia were found to fall into three different groups: (1) congenital pneumonia; (2) aspiration pneumonia, and (3) pneumonia of undetermined origin. *Congenital pneumonia* develops in the fetal lung during intrauterine life as the result of aspiration of amniotic fluid which has become infected, usually as a sequelae to premature rupture of the membranes. This is the type of pneumonia which occurs most frequently in the term infants (46 per cent). The train of events which leads to aspiration of infected amniotic fluid are the same as those which are followed by aspiration of noninfected fluid. *Aspiration pneumonia* resulting from inhalation of vomitus or food was seen most frequently among the premature infants. Eighty per cent of the pneumonias occurring among the viable premature babies were of this type. *Pneumonia of bacterial origin* occurred less frequently (20.8 per cent). The types seen were usually bronchopneumonia or a patchy disseminated bronchopneumonia. The incidence of this type of pneumonia was almost twice as frequent in the term babies as in the premature group.

Hemorrhage: was the third most frequently encountered lung lesion (10.2 per cent). Massive hemorrhage of the lungs accounted for 4.7 per cent of the deaths among the term infants and 1.25 per cent of the deaths among the viable premature group. Only the extensive forms of pulmonary hemorrhage were listed in this group. Mild patchy areas of hemorrhages frequently seen in premature infants or in association with intrauterine asphyxia were not considered of primary importance.

Massive pulmonary hemorrhage may develop if, with the occurrence of fetal asphyxia, respirations are initiated while the head is in the vaginal passages. During the passage of the head through the vagina, the mucous membrane is closely approximated to the mouth of the fetus. Attempts to breathe during this stage results in the production of a negative intrathoracic pressure. When all of the muscles of respiration come into play, the negative pressure becomes so great that engorgement of the alveoli takes place with subsequent rupture of the alveolar septa and blood vessels. This condition may also result from too energetic attempts at resuscitation.

Hyaline Membrane: This lesion was seen in four premature infants (5.9 per cent). The exact etiology of this condition is unknown. Its formation may represent a late effect of intrauterine aspiration of amniotic fluid occurring well in advance of labor and delivery. In the succeeding antenatal period the fluid is absorbed but the solid elements of the aspirated amniotic fluid become altered to form a hyalinized gummy substance. This material blocks the opening of the alveolar sacs, prevents their expansion and is responsible for the dilatation of the alveolar ducts characteristic of this condition. This causes embarrassment to respiration, due to interference with the normal diffusion of gaseous elements in the alveolar spaces and to the inefficiency of such exchange through the walls of the alveolar ducts.

III. *Birth Trauma*.—The third largest cause of death was from birth trauma (16.9 per cent). Thirty-two and nine-tenths per cent of the term and 12.8 per cent of the viable premature infants died because of injury.

The types of injuries encountered were found to fall into three main groups: (1) intracranial; (2) spinal; and (3) intra-abdominal. In some instances, intracranial injuries were found associated with spinal or intra-abdominal injuries (Fig. 3).

The intracranial injuries consisted of lacerations of the dural septa, subdural hemorrhage usually due to rupture of the great cerebral vein or its tributaries, subarachnoid hemorrhages and subventricular hemorrhages. Lacerations of the dural septa (falx cerebri and tentorium) and subdural or subtentorial hemorrhages were the lesions most commonly found in the term

of the cases. Anoxemia, prematurity, birth trauma, maceration, congenital anomalies and infections (mostly pneumonia) were listed as the main causes of death. Cruickshank⁴ (1930) also found that 67.5 per cent of babies died of prematurity, asphyxia, and birth trauma; 29.7 per cent of infections; and 2.7 per cent of major congenital anomalies. Others have agreed that these lesions were the major causes of fetal and neonatal deaths.¹⁵

The present study confirms these findings, although due to differences in classification of the causes of death the findings appear to be at variance with these previous reports. We have attempted to avoid a mixture of physiologic and anatomico-pathologic terms in classifying the causes of neonatal deaths. Thus the term asphyxia, which denotes a physiologic state in utero, has been supplanted by anatomic terms describing the pathologic lesion which resulted from the asphyxial state and which was considered as being the major anatomic cause of death. Due to the asphyxia resulting from placental hemorrhage, prolapse of the cord or knot in the cord, maternal infection, or toxemia, deep inspiratory movements of the fetus are initiated in utero. As a direct result of this, the amniotic fluid contains many epithelial cells desquamated from the skin of the fetus. These cellular elements are found in large numbers in the lung alveoli and serve as the basis for the anatomic diagnosis of aspiration of amniotic fluid. Other minor anatomic evidences of the asphyxial state will be found also, such as congestion of all viscera and small hemorrhages of the brain and lungs. Not all asphyxiated babies will die in utero, but many of those that survive intrauterine life will die in the neonatal period as an aftermath of aspirated amniotic fluid which occurred in utero. Due to the flooding of the alveoli, proper gaseous interchange is impossible, and thus the asphyxial state beginning in utero continues in the neonatal period with the production of cyanosis and convulsions. The latter symptoms frequently lead to the erroneous diagnosis of birth trauma.

In the event that the amniotic fluid has become contaminated with a purulent exudate due to an amniotic sac infection, intrauterine asphyxia will result in the aspiration of infected amniotic fluid. Microscopically, examination of the lungs shows the alveoli to contain not only desquamated epithelial cells, but also large amounts of purulent exudate and many bacteria. Because this pneumonia originates while the fetus is in utero due to aspiration of infected amniotic fluid, this lesion has been termed a congenital pneumonia.

The term atelectasis has been avoided because it is not an anatomic cause of death.^{1, 15} While it may be present, the underlying cause which results in this condition such as prematurity, birth trauma, and aspiration of foodstuff or vomitus should be considered the primary cause of death.

Table V has been prepared comparing our findings of the causes of fetal and neonatal deaths with those of two recent studies. The causes of death as reported in the preceding pages have been rearranged to conform with the nomenclature used by these authors. When this is done, the close similarity of the major causes of fetal and neonatal deaths in all three reports becomes apparent.

vital organs were taken and stained with the Levitidi stain to determine the presence of spirochetes, and microscopic study of the bone was done to detect the presence of syphilitic osteochondritis.

An attempt has been made to correlate the death of the fetus and subsequent maceration with some clinical maternal disorder occurring during the prenatal period or labor (Fig. 4). In over one-half of the cases of maceration (55.2 per cent) no maternal cause for death of the fetus could be determined. Since most of these deaths occurred during the years before knowledge of the Rh factor, it is impossible to state whether some of these macerated stillbirths may have been due to erythroblastosis. In the remainder, however, some maternal abnormality was present. Toxemia was the most frequent maternal complication (21 per cent) which apparently resulted in death of the fetus in utero. Vaginal bleeding, most frequently due to premature separation of the placenta, was followed by death of the fetus and was the complicating prenatal factor in 11.8 per cent. Of the 46 macerated fetuses, born of mothers suffering from toxemia or premature separation of the placenta, 38 were premature.

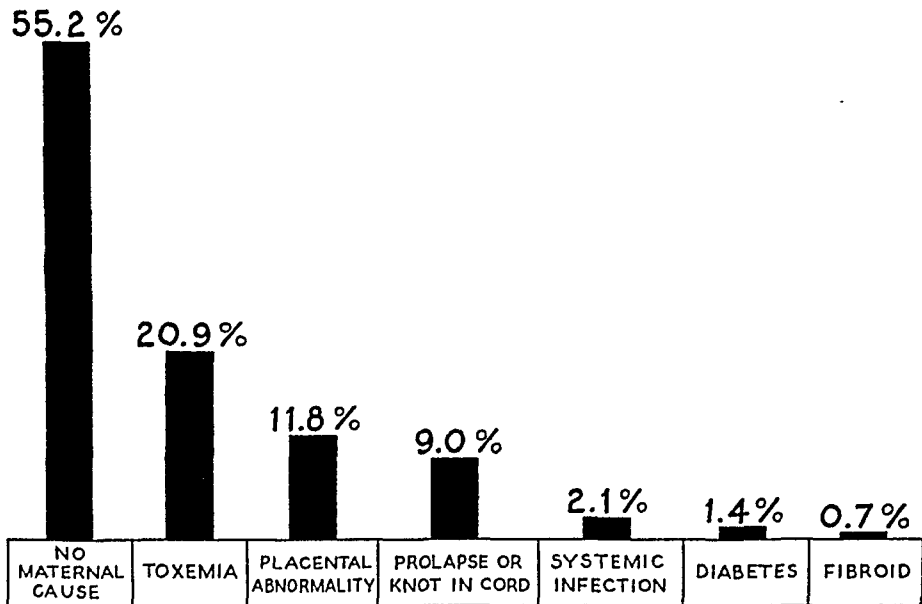


Fig. 4.—Complications of pregnancy associated with macerated stillbirths.

Obstruction of the umbilical cord by knots, prolapse or excessive winding about the fetus was found in 9.1 per cent of the cases of maceration and nine of these thirteen stillbirths were full term.

Rupture of the uterus (1 case), severe maternal infections (3 cases), fibromyomata uteri (1 case), and diabetes mellitus (2 cases) were among the remaining maternal conditions.

V. *Other Causes of Death.*—Space does not permit a detailed account of other causes of neonatal and fetal deaths. The incidence and the relative frequency of these conditions may be seen in the accompanying tables.

Comment

In recent years two studies of the causes of the fetal and neonatal deaths have been reported.^{5, 11} Each of these included over one thousand fetal and neonatal deaths with postmortem examination performed in almost 90 per cent

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Discussion

DR. D. ANTHONY D'ESOPPO.—Dr. Labate approached the subject of asphyxia from the point of view of the pathologist, and avoided the term asphyxia which Dr. Marchetti and I used in our paper. This was used synonymously with the term "aspiration of amniotic fluid." The diagnosis of aspiration of amniotic fluid can be made only from pathological study and since not all of our cases were examined postmortem, the clinical term, asphyxia, was used.

Dr. Labate's slide showing the pathology of aspiration of amniotic fluid was interesting and typical. There are other lesions that go with aspiration of amniotic fluid, or asphyxia, which I think should be stressed, namely, the marked congestion that takes place throughout the entire body of the infant; the blood vessels are dilated, and this is apparent not only macroscopically in the viscera, but also in all the microscopic sections. That point is interesting to me because recently in studying cases of birth injury we have been impressed with the frequency of the two conditions, namely, birth injury and asphyxia. I am sure that anybody who does newborn pathology will frequently see these two conditions associated. Sometimes it is difficult to tell which is the primary condition, that is, whether the child originally was subjected to birth trauma and as a result of that became asphyxiated, or whether the child was primarily anoxic and in the course of delivery was subjected to birth trauma. I wonder if the congestion, the marked engorgement of large blood vessels, which I think is such an important part of the associated pathology of anoxia, may not to a large extent contribute to birth trauma. Where there is marked engorgement or congestion of the vagina, injuries such as sulcus tears may easily occur with instrumental deliveries.

I wonder if the intracranial structures are not more easily injured when we have a baby who is suffering from anoxia. There is a tendency to rush the delivery of a child suffering from anoxia because of the fear that further anoxia will kill the baby. I believe that frequently in speeding the delivery we subject the baby to a considerable degree of trauma and as a result produce birth injuries.

DR. MORTIMER D. SPEISER.—It might be well to mention in connection with the prophylaxis of congenital pneumonia, the possible value of the routine employment of substances such as penicillin after the membranes are ruptured in order to avoid the consequences of congenital pneumonia.

TABLE V. COMPARISON STUDIES OF NEONATAL MORTALITY

| | POTTER AND ADAIR | D'ESOPO AND MARCHETTI | LABATE |
|----------------------------|------------------------|-----------------------------|---|
| Prematurity | 25.6 | 18.5 | 27.6 |
| Anoxia | 28.7 | 19.8 | 17.9 (aspiration amniotic fluid 13.6%. Aspiration of infected amniotic fluid— congenital pneumonia 1.6. Hemorrhage of lung 2.3%. Hyaline membrane of lung 0.4%) |
| Birth trauma | 13.0 | 11.6 | 16.9 |
| Maceration | 17.2 | 18.7 | 16.5 |
| Major congenital anomalies | 11.1 | 14.1 | 7.4 |
| Infections | 4.7 | 8.1 | 6.1 |
| Erythroblastosis | 2.5 | 2.8 | 1.7 |
| Syphilis | 0.2 | 0.6 | 4.5 |

An analysis of the causes of fetal and neonatal death is valueless unless conclusions can be drawn therefrom which will prevent fetal and neonatal deaths and thus improve the mortality rate. The death rates from prematurity, pulmonary lesions, and birth trauma, which constitute the three major causes of death, can be greatly improved. Similarly, fetal death from syphilis, infection, and erythroblastosis is preventable to a considerable degree.

Table II shows the reduction in the term and premature death rate at Bellevue Hospital during a nine year period. This decline in the death rate is largely due to the precautions which have been taken to prevent the occurrence of the major conditions which were found to have produced death of these infants. The lessons learned at the autopsy table have been carried to the delivery room and the nursery. The fetal and neonatal death rate for the country at large could be reduced equally well if the profession generally were to be made more conscious of the causes of this mortality.

Summary

1. An analysis of the cause of death has been made, based on the study of 868 autopsies performed during a ten-year period beginning July 1, 1933.
2. Prematurity, pulmonary lesions, and birth trauma were the three highest causes of death.
3. The main causes of fetal death in the term and premature infants and certain aspects of their prevention have been discussed.

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eight hours of a single subcutaneous injection was considered the minimal lethal dose (M.L.D.). The toxicity of the total output for one period of young women with regular cycles and no excessive flowing was fairly uniform, the M.L.D. lying between 0.05 and 0.2 c.c. of whole discharge. It was soon discovered, however, that separate specimens from the same individual during a given menstrual period varied considerably. The greatest toxicity appeared to be in specimens collected early, when flow was scanty, and the least in specimens obtained when bleeding was profuse. Whole discharge from a patient with dysfunctional flowing could be shown to contain the toxin only if the material was concentrated by extraction (v.i.). The explanation for these observations was revealed when we began centrifuging the whole discharge and testing separately the supernatant "serum," the bottom layer of red blood cells, and the middle grayish layer containing endometrial debris. The washed red blood cells were found to be practically nontoxic, whereas the "serum" from a normal menstruation was always lethal in 0.1 to 2 c.c. amounts, and the washed endometrial debris, suspended in saline for injection, contained the greatest concentration of the toxin, being lethal in amounts equivalent to 0.005 to 0.1 c.c. The toxicity of various specimens of whole discharge was then discovered to be directly proportional to the amount of endometrial debris, specimens collected during scanty flow at the start of menstruation containing the greatest proportional amounts of debris, and those from cases of dysfunctional flowing containing the least. It appeared, therefore, that the endometrial debris was the source of the toxin. This was confirmed by the demonstration that fresh endometrium obtained directly from the uterus just before or during menstruation was lethal to rats in 50 to 100 mg. amounts (wet weight), whereas 200 to 300 mg. of endometrium taken at other times were nontoxic. The concept was tenable, therefore, that the premenstrual withdrawal of hormonal support permits catabolic changes in the endometrium which result in the formation or release of a highly toxic material. The variability in the amount of endometrial debris, and of toxicity, in various specimens indicated that postovulatory flow was associated with a more profuse release of toxin and shedding of endometrial tissue than pertained when bleeding was the result of estrogen withdrawal only. From this we would conclude that, although estrogen deprivation causes release of the same toxic factor as that present at postovulatory bleeding, previous stimulation of the endometrium by progesterone results in release of larger amounts of toxin.

Extraction of Toxin from Menstrual Discharge

In concentrating the toxic factor from menstrual "serum" or whole discharge, we used fractional salting-out with $(\text{NH}_4)_2\text{SO}_4$ and found that all of the toxicity was recovered in the water-insoluble portion after dialysis of the euglobulin precipitate that was brought down by one-third saturation with $(\text{NH}_4)_2\text{SO}_4$. We observed that this precipitate was not entirely soluble in physiologic saline, as are normal serum euglobulins, and that if the saline suspension was centrifuged until the supernatant was clear, all of the toxicity was

MENSTRUAL TOXIN

I. Experimental Studies*

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FROM the accumulated bulk of experimental evidence it appears clear that only two factors are essential for endometrial bleeding in the primate; an endometrium and withdrawal of hormonal support, either estrogen alone or estrogen and progesterone. The classical researches of Markee¹ on the behavior of blood vessels in intraocular transplants of monkey endometria and the histologic studies of Bartelmez² on human uteri have revealed profound and characteristic vascular changes to be constant and immediate precursors of endometrial bleeding. The sequence of these changes is the same whether the endometrium has been previously stimulated by estrogen alone or by estrogen and progesterone. In the final analysis, therefore, of all the theories on the cause of menstruation that have been proposed, the only one that still seems to hold is that of estrogen deprivation, first propounded by Edgar Allen in 1927.³

Nevertheless, a number of writers have questioned the adequacy of the withdrawal theory. Hartman and Firor⁴ have raised numerous objections based upon their observations in monkeys. They feel that some extraovarian factor must be involved and, considering "the potency of infinitesimally minute quantities of chemical substances in their vasomotor action," have suggested that the answer may lie in the field of pharmacology rather than endocrinology. Engle⁵ has voiced similar doubts and states that "it may be a mistake to say that the withdrawal of one of the hormones *causes* menstruation; rather such a lack of hormone *permits* changes in the endometrium and blood vessels, which result in the bleeding."

A similar line of thought led us to study the menstrual discharge itself with the idea that the "bleeding factor," if it existed, must originate locally and might be present in this material. Macht⁶ had previously found in the sweat, saliva, and circulating blood of menstruating women a substance toxic to plant growth. No other scientific evidence had been reported, however, to indicate that menstruation might be a toxic phenomenon, although folklore from as far back as biblical times has considered it such.

The Toxicity of Menstrual Discharge

In our earliest work, published in 1940,⁷ we first tested pooled specimens from a complete menstrual period, the whole unextracted discharge being used. For measuring toxicity the immature male rat (nineteen to twenty-one days old) was employed, and the smallest amount that caused death within forty-

*Presented on Jan. 25, 1947, at a conference on Menstruation and Its Disorders sponsored by the National Committee on Maternal Health.

removes the euglobulins that may be precipitated by one-third saturation with $(\text{NH}_4)_2\text{SO}_4$ as well as the toxin, we may still be correct in assuming that the toxin is a large moleculated, euglobulin-like material. It differs from the euglobulins of normal serum, however, in that it is insoluble in physiological saline. From the previously observed findings, we feel sure that bacteria are not responsible for the toxicity of menstrual discharge, and the very fact that Seitz filtration removes the toxic factor argues against the possibility that toxic products of bacterial action are involved.

The Pathologic Action of Menstrual Toxin

The pathological effect of menstrual toxin upon the immature rat is one of generalized tissue and pronounced vascular damage.^{7, 8} The injection is given subcutaneously in the nape of the neck. Within twelve hours the animal shows a bloody discharge from the eyes and the nose and a pronounced girdle of edema through the chest and axillary region. Within twenty-four hours the animal is usually "dead on its feet," but may keep breathing for another ten to twenty hours if a minimal lethal dose has been injected. Autopsy at this time reveals bloody edema throughout the axillary region, a mottled appearance in the liver, swollen, pale kidneys, and enlarged, purple adrenals, these being the most characteristic, grossly-apparent abnormalities. The urine is always concentrated, indicating water retention, and sometimes bloody. Doctor Arthur T. Hertig has kindly consented to discuss the microscopic pathology resulting from menstrual toxin at the end of our papers. That the pathologic changes are the result of vasoconstriction and local stasis is indicated by the fact that the intracutaneous injection of tiny amounts of the toxin into rabbits prevents the appearance of intravenously administered trypan blue in that area, and keeps the dye from diffusing from that area if it is intracutaneously administered there. The menstrual process as actually observed by Markee in endometrial transplants into the monkey's eye suggests the local release of some vasoconstrictor material. In fact, Markee⁹ has recently demonstrated that a so-called "necrosin-like" substance similar to if not identical with our menstrual toxin (v.i.) causes constriction of the coiled arteries in intraocular endometrial transplants and concludes that the vasoconstriction which begins four to twenty-four hours before the start of bleeding and persists throughout it is controlled by such a substance.

Menstrual Toxin and Canine "Necrosin"

The fact that the toxin of menstrual discharge appeared to be derived from the cast-off endometrium indicated that it might be a product of the tissue catabolism which results from withdrawal of hormonal support. Throughout our studies we have been imbued with the idea that tissue catabolism from causes other than hormonal and in sites other than the endometrium might involve the release of a similar toxin. Negative results were acquired in our numerous attempts to recover a toxic protein from various parts of the anatomy of rats, rabbits, and guinea pigs after partial blocking of the circulation. One of the reasons why we were anxious to obtain the toxic factor from other than

concentrated in the saline-insoluble precipitate. We therefore concluded that the toxic factor either was, or was closely associated with, an atypical euglobulin. Saline suspensions of the water-insoluble precipitate after dialysis were used for tests, and, when fresh, were lethal in amounts equivalent to the M.L.D. of the original "serum" or whole discharge. This is the method still used by us for concentrating menstrual toxin. The toxic factor, however, is extremely labile, especially after this partial purification. It is destroyed by prolonged dialysis (over seven hours against running tap water), by hydrogen ion concentrations above seven or below six, by temperatures above 45° C., and by organic solvents sufficient to precipitate proteins. In aqueous suspension toxicity disappears fairly rapidly, even if kept at temperatures below freezing. The only means by which the original toxicity of unextracted menstrual "serum," of whole discharge or of euglobulin precipitates may be preserved is by immediate and rapid freeze-drying.

Specificity of the Toxin of Menstrual Discharge

Hemolysis is always quite pronounced in menstrual discharge. The possibility that toxicity might be due to products of hemolysis, however, was eliminated by the demonstration that toxicity comparable with that of menstrual "serum" could not be produced by hemolysis of the red blood cells of the same specimen. Furthermore, repeated washings of the endometrial debris of menstrual discharge with physiologic saline until all the color of hemoglobin was removed did not decrease the very marked toxicity of this fraction. The possibility that bacterial contamination accounted for toxicity was, of course, considered. If bacterial action were involved, one would expect an increase in toxicity upon standing at room temperature. Early in our investigations, however, it was discovered that unless each collection was refrigerated immediately, toxicity would disappear rapidly. Furthermore, sterile scrapings of menstruating endometrium gave the typical reaction and death in test animals. Finally, the incubation of normal venous serum inoculated with menstrual discharge did not produce toxicity comparable with that of the discharge itself.

Because the evidence seemed to us sufficient to rule out bacteria, alive or dead, as responsible for the toxicity of menstrual discharge, it was not until recently that we tested the effect of Seitz filtration. The "serum" of menstrual discharge is a thick, viscous fluid which, even after prolonged centrifugation, is never clear. Because of its content of mucoid material, it can be filtered only through a fast filter paper, giving a cloudy filtrate. From a 60 c.c. sample of "serum" we were able to get only 10 c.c. through a Seitz filter. What came through was thin, crystal clear, and nontoxic in five times the M.L.D. of the original discharge. In attempting to concentrate this filtered "serum" we were surprised to discover that no precipitate came down upon one-third saturation with $(\text{NH}_4)_2\text{SO}_4$. The "serum" from centrifuged discharge gives a very heavy precipitate at this point, much more than is obtained by one-third saturation of venous serum. This observation leads us to wonder if the toxin of menstrual discharge may not be contained in or adsorbed upon a suspended protein aggregate. Since the removal of this aggregate by Seitz filtration also

ficiently purified so that nonspecific human and canine proteins, respectively, have been eliminated. The fact that both produce the formation of precipitin antibodies against themselves, therefore, is without significance. The demonstration, however, that the serum of a rabbit immunized against menstrual toxin precipitates canine "necrosin" and vice versa supplies strong evidence for an identical protein factor in these two materials.¹¹ These cross precipitin experiments were few in number and require further confirmation. Recently we have been attempting to do this, but have had considerable difficulty in recovering enough necrosin from canine pleural exudates to produce a high enough titer of antibodies to give clear-cut results. For this same reason, our original hope that necrosin-immune rabbit serum would provide an antitoxin for menstrual toxin that was free of nonspecific antibodies to human proteins has had to be abandoned. Unless the precipitin antibody titer is as high as 1:1,000,000, transferable immunity is not demonstrable. This we have never been able to acquire in necrosin-treated rabbits, although such a titer against menstrual toxin is easily produced. As stated above, the serum of an animal thus immunized against menstrual toxin protects an immature rat against an otherwise lethal dose of menstrual toxin. The same serum affords equally good protection against a lethal dose of canine necrosin.

The apparent identity of the product of endometrial breakdown after withdrawal of hormonal support with a protein substance released from cellular injury related to an inflammatory process strengthens the concept that tissue catabolism from various causes may involve the production or release of such a toxin, thus relating this factor, possibly, to the clinical syndrome of burns, crush syndrome, shock, postoperative morbidity, etc., as well as late pregnancy toxemia, the various clinical pictures depending upon the amount and duration of formation and absorption of toxin. The fibrinolytic activity of menstrual discharge suggested to us that the toxin might be an intermediary product of the action of a proteolytic enzyme released by tissue injury. We now have reason to believe, however, that toxin and enzyme may be identical. Possibly the toxin and/or enzyme and the protective pseudoglobulin are split-off components of cells in the process of tissue catabolism.

Menstrual Toxin in the Circulating Blood

Early experiments convinced us that there was not enough toxin in the circulating blood at the time of menstruation to be demonstrable by our test for the lethal action in immature rats. Our more recent studies of the characteristics of menstrual discharge supplied us with more sensitive tests, and we have found that the circulating blood of normal women at the time of menstruation differs from that collected between catamenia and resembles menstrual discharge in that it contains, in the euglobulin fraction, fibrinolytic and pyrogenic activity (as tested on rabbits) and, in the pseudoglobulin fraction, a substance capable of prolonging the survival time of rats given a minimal lethal dose of menstrual toxin.¹⁵ We have also found these same properties to characterize the venous blood of pregnant women suffering from late pregnancy tox-

human sources was because we had shown that immunity to menstrual toxin could be produced by repeated injections of sublethal amounts, and that the serum of an immunized rabbit prevented death in a rat given an M.L.D. of toxin.⁸ We were thinking of this in relation to the treatment of late pregnancy toxemia, since we already had reason to believe that the same toxin was operative in this disease. Serum from a rabbit immunized against menstrual toxin could not, of course, be given to human beings because of the content of non-specific antibodies to human protein. The production of the same toxin in other species, therefore, had practical possibilities from the clinical aspect.

While we were engaged in studies along this line, a preliminary report by Menkin appeared in *Science*¹⁰ describing an injury factor in the pleural exudate of dogs following the inflammatory reaction caused by turpentine. Many points of similarity between his so-called "necrosin" and our menstrual "toxin" suggested that we were dealing with the same material. Among others, "necrosin" was very labile and concentrated in the euglobulin fraction, being, however, an atypical euglobulin, since it was not soluble in the presence of electrolytes. In attempting to prepare necrosin ourselves according to Menkin's specifications, we discovered that the euglobulin fraction of canine pleural exudate frequently has no demonstrable amount of toxicity, by our test, and never contains concentrations that compare with those in menstrual discharge. However, by fractionation of this material we were able to get enough to perform experiments which gave good indication that canine pleural exudates and human menstrual discharge contain an identical toxic factor. The pathologic effects of necrosin were found to be entirely similar to those of menstrual toxin, although much more pleural exudate must be used to demonstrate toxicity in rats.¹¹ The euglobulin fraction of menstrual discharge is markedly fibrinolytic as well as toxic.¹¹⁻¹³ We found canine "necrosin" also to have this property,^{11, 12} and Menkin gives reference to unpublished findings of his own which confirm this.¹⁴ The pyrogenicity of the euglobulin fraction of canine pleural exudate as tested on rabbits¹⁴ was also demonstrable with menstrual toxin.¹¹ We have been unable to separate the pyrogenic factor from the toxin of menstrual discharge, although Dr. Menkin believes that in pleural exudate they are different entities. Our own feeling is that the elevation of temperature observed in the rabbit is the usual response of that species to nonspecific, injurious stimuli. We have been unable to affect the body temperature of rats or guinea pigs with either "necrosin" or menstrual toxin. In the pseudoglobulin fraction of menstrual discharge we have found a factor capable of prolonging the survival time of rats given a lethal dose of menstrual toxin.¹¹ We discovered that this same fraction protects rats against canine "necrosin" and that the pseudoglobulin fraction of pleural exudates, both human and canine, protects against menstrual toxin.^{11, 15} This finding has had practical implications which will be discussed further.

The most direct evidence for the similarity of the toxic protein of menstrual discharge and of canine pleural exudate has been gained by immunologic experiments. Neither menstrual toxin nor Menkin's "necrosin" have been suf-

pears to originate in the fetus and the observations suggest that it is proportional to the degree of anoxemia. Furthermore, the pseudoglobulin fraction of fetal blood is markedly protective against menstrual toxin.

TABLE II. FIBRINOLYTIC ENZYME IN MATERNAL VS. FETAL SERUM AT TIME OF DELIVERY*

| | MATERNAL | | FETAL | | | |
|-------------------|----------------|----------------------|----------------|----------------------|----------------|----------------------|
| | NUMBER SERA | PER CENT POSITIVE | VENOUS | | ARTERIAL | |
| | | | NUMBER SERA | PER CENT POSITIVE | NUMBER SERA | PER CENT POSITIVE |
| Spontaneous labor | | | | | | |
| 1-7 hours | 3 | 0 | 3 | 0 | 3 | 67 |
| Induced labor | | | | | | |
| 2-5 hours | 3 | 100 | 3 | 67 | 3 | 67 |
| Spontaneous labor | | | | | | |
| 18-39 hours | 4 | 100 | 4 | 75 | 4 | 100 |
| Elective cesarean | | | | | | |
| no labor | 5 | 0 | 5 | 100 | 4 | 100 |

*These experiments were performed in collaboration with Drs. Clement A. Smith, Duncan E. Reid and Charles C. Robey of the Boston Lying-In Hospital, Dr. Robey having collected the maternal and fetal bloods for study.

Are Toxin and Enzyme Identical?

Although quantitative tests have not been performed, the amount of enzyme appears to be roughly proportional to the amount of toxin present in the material tested. As little as 0.005 c.c. of unextracted "serum" from menstrual discharge will give complete dissolution of a fibrin clot in twenty-four hours; whereas more pleural exudate is required and the serum of circulating blood has to be concentrated in order to give a positive test by this method. The fibrinolytic activity of the blood of patients with late pregnancy toxemia is, in general, more marked than that in the circulating blood of menstruating women (Table I), and appears to be related to the severity of the disease. Furthermore, the administration of the protective pseudoglobulin to both pregnant and non-pregnant patients whose blood contains fibrinolytic activity causes a marked reduction or disappearance of the enzyme, this effect being associated with alleviation of toxic signs. Further details on this subject will be presented by Dr. George V. Smith. These observations have led us to wonder if enzyme and toxin may not be identical. On the other hand, human plasma treated with chloroform according to the method of Tagnon and Taylor¹⁷ is as markedly fibrinolytic as menstrual discharge, but contains no demonstrable amount of toxicity. (It also contains no protective pseudoglobulin, much to our disappointment.)

Source of the Protective Factor for Clinical Trials

The most practical as well as the richest source of this factor has been human exudative material from any inflammatory process. During the last eight months we have obtained from eight patients with metastatic carcinoma nearly 70 liters of pleural or abdominal fluid. The pseudoglobulins have been partially purified and concentrated by fractional salting out with $(\text{NH}_4)_2\text{SO}_4$ and the final preparation passed through a Seitz filter into sterile vials. This

emia.¹⁵ In the serum of normally pregnant women they are demonstrable only during labor. Our few observations on the presence of precipitin antibodies to canine necrosin immune rabbit serum in the circulating blood of menstruating and toxemic women¹⁵ require further confirmation. The fibrinolytic activity of venous serum of toxemic as opposed to normal pregnancies has recently been confirmed by Willson and Munnell.¹⁶

Since our last publication on the subject,^{11, 15} we have continued testing various types of circulating blood for fibrinolytic enzyme, utilizing the method in which the euglobulins from 5 c.c. of serum are concentrated for test against a standard fibrin clot.¹⁵ An essential part of this method is establishing the smallest amount of fibrinogen and thrombin in the preparations used which, in the absence of any added fibrinolysin, will give a clot that remains stable during the twenty-four-hour incubation period. A control must be run for each series of observations. Previously unpublished results on untreated women are summarized in Table I. Our earlier observations are confirmed and it is apparent that the presence of the enzyme is associated with cellular injury from causes other than hormonal, as, for example, infectious, cancer and postoperative morbidity. The most striking results have been with sera from women suffering from pre-eclampsia and eclampsia and in specimens collected at delivery after a prolonged labor.

TABLE I. FIBRINOLYTIC ENZYME IN THE CIRCULATING BLOOD OF WOMEN

| CONDITION OF PATIENT | NUMBER OF PATIENTS | NUMBER OF SERA | DISSOLUTION OF FIBRIN CLOT % OF TESTS SHOWING: | | |
|---|--------------------------|----------------------|---|---------|------|
| | | | COMPLETE | PARTIAL | NONE |
| <i>A. Nonpregnant</i> | | | | | |
| Normal—not flowing | 11 | 17 | 0 | 0 | 100 |
| Flowing { Normal cta. | 6 | 10 | 13 | 87 | 0 |
| | { Pathologic | 5 | | | |
| Infections (pelvic abscesses, etc.) | 5 | 6 | 0 | 83 | 17 |
| Invasive cancer (not flowing) | 3 | 3 | 0 | 100 | 0 |
| Prolapse of uterus { before operation | 3 | 3 | 0 | 0 | 100 |
| | { 2 days postoperative | 3 | 0 | 100 | 0 |
| <i>B. Pregnant—During Second or Third Trimester</i> | | | | | |
| Pregnancy normal | 6 | 13 | 0 | 0 | 100 |
| Pre-eclampsia or eclampsia | 11 | 24 | 71 | 29 | 0 |
| <i>C. Pregnant—at Delivery</i> | | | | | |
| Elective Cesarean | 5 | 5 | 0 | 0 | 100 |
| Spontaneous labor (1-7°) | 3 | 3 | 0 | 0 | 100 |
| Induced labor (2-5°) | 3 | 3 | 33 | 67 | 0 |
| Spontaneous labor (18-39°) | 4 | 4 | 100 | 0 | 0 |

In the studies on blood at delivery we also ran determinations upon the fetal blood, i.e., blood collected from the umbilical vein and artery (Table II). These are of interest in connection with the possible mechanism of formation and release of the enzyme. Fibrinolytic activity was more marked in the arterial than in the venous umbilical blood and bore no constant relationship to the amount of circulating enzyme in the mother. Thus, in elective cesarean sections no activity was demonstrable in the maternal blood, whereas the tests on fetal blood were all positive. In other words, the enzyme in the fetal circulation ap-

reaction had no effect on adrenal or pituitary weights, but caused a significant decrease in the transplantable adrenotropic and gonadotropic activity of the pituitaries, indicating release of both of these factors. When a toxic but sublethal daily dosage was given for five days, enlargement of the pituitaries as well as of the adrenals resulted, together with a decrease in transplantable adrenotropic activity and an increase in the content of gonadotropic hormone. From these observations it would appear that menstrual toxin (and probably any noxious stimulation) may, in a single overwhelming dose, have a direct effect upon adrenal weight. In sublethal dosages over longer periods, pituitary gonadotropic as well as adrenotropic activity is influenced, the indications being that both release and increased stimulation of gonadotropic activity may result, the type of response being dependant upon the amount given and the duration of treatment. These findings seem to us to give the "adaptation reaction" even more physiologic significance than is ordinarily attributed to it, since the reproductive organs as well as the adrenals appear to be influenced.

Conclusion

Although the studies on menstrual toxin that I have presented cover a period of eight years, it is apparent that much work remains to be done. Certain properties of menstrual discharge have been established, the most important being a toxic factor and a fibrinolytic enzyme associated with the euglobulin fraction, and a substance in the pseudoglobulin fraction which neutralizes the toxin. These same properties have been demonstrated in the circulating blood of women during menstruation, late pregnancy toxemia and prolonged labor but not in that of nonmenstruating or normally pregnant women. They have also been demonstrated in exudative material from inflammatory reactions, indicating that, although in the menstruating endometrium and in toxemia of pregnancy they result from tissue catabolism due to withdrawal of hormonal support, other sorts of cellular injury may cause a similar phenomenon. At present, however, they can only be called "properties," since neither the mechanism of their formation, other than that it appears to be a part of tissue catabolism, nor their chemical nature, other than that they are associated with protein materials, has been established. Thus far we have only been scratching the surface in an attempt to gain some further understanding of menstruation and of late pregnancy toxemia and in the hope of gaining knowledge that would be of clinical value. We would be delighted if the pathologists, the immunologists and the protein chemists would consider our pioneering efforts worthy of their more refined methods of investigation.

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relatively crude method of preparation gives good yields of the protective factor in a slightly cloudy, greenish fluid, which, although some preparations cause local soreness, has never produced any systemic reactions when intramuscularly injected. We would like to concentrate and purify this factor further, both for clinical purposes and with the aim of learning more about the nature of this substance.

The Pituitary Stimulating Properties of Menstrual Toxin

In our earliest work on menstrual discharge it was discovered that this material stimulated the production of functional corpora lutea in mature female rats,¹⁸ as well as causing pronounced adrenal enlargement.⁷ This finding was not emphasized, since we were later informed by Dr. E. B. Astwood that he, in unpublished work, had observed the same phenomenon as a result of any injurious stimulation. Various investigators have confirmed Selye's¹⁹ original observation of adrenal enlargement in rats following noxious stimuli, and have shown this reaction to be mediated by the pituitary. So far as we know, however, Dr. Astwood and ourselves are the only observers who have noted the stimulation and release of gonadotropic as well as adrenotropic hormones from the pituitary as a part of the "alarm" reaction. This effect has been recently confirmed by experiments upon mature male rats whose adrenals and pituitaries were weighed following injections, and the pituitaries transplanted into immature females to test their content of adrenotropic and gonadotropic hormones (Table III). The administration in a single injection of an amount of toxin sufficient to kill these animals caused an immediate enlargement of the adrenals but no demonstrable effect upon the pituitaries, except a questionably significant decrease of adrenotropic activity. The daily administration for three days of an amount that produced very little clinically apparent toxic

TABLE III. EFFECT OF MENSTRUAL TOXIN UPON THE ADRENALS AND PITUITARIES OF INTACT MATURE MALE RATS

| ADMINISTRATION OF TOXIN* | AUTOPSY HOURS AFTER LAST INJEC- TION | NUM- BER OF RATS | AVERAGE PER CENT CHANGE VS. LITTERMATE CONTROL† | | | | |
|---|---|---------------------------|--|---------------------|---------------------------------|-------------------|--|
| | | | ADRENALS WEIGHT | PITUITARY WEIGHT | TRANSPLANTABLE ACT. OF PIT.‡ | | |
| | | | | | ADRENO- TROPIC | GONADO- TROPIC | |
| (1) 400 mg. in 1 injection | 24° | 4 | +64 ± 10 | +1.3 ± 2 | -10 ± 3 | +0.5 ± 2 | |
| (2) 100 mg. in 6 injections over 3 days | 16° | 4 | +0.5 ± 4 | +9.7 ± 3 | -21 ± 2 | -37 ± 5 | |
| (3) 400 mg. in 10 injections over 5 days | 16° | 5 | +52 ± 9 | +21 ± 2 | -22 ± 4 | +42 ± 5 | |
| Control rats (littermate vs. littermate) | | 10 | +2.1 ± 3 | +0.9 ± 4 | -1.7 ± 4 | +0.7 ± 2 | |

*Seventy-five mg. = M. L. D. for 19d., 25 Gm. male rats. The animals in group (1) were moribund at autopsy; those in group (2) were well except for slight subcutaneous induration at the site of injections; those in group (3) had lost weight, were apathetic and had severe local reactions at the site of injections.

†For each experimental animal a control littermate of the same weight (± 5 Gm. was simultaneously autopsied. All animals were 80 to 100 days old and weighed 150 to 200 Gm.

‡Pituitaries were ground in saline and injected in 6 injections over 3 days into 19- to 21-day-old female rats whose ovaries and adrenals were weighed on the 5th day. For each experimental pituitary recipient, a control littermate of the same weight was run that received the pituitary of an uninjected littermate donor.

MENSTRUAL TOXIN

II. Clinical Significance*

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THE finding of a toxic protein in the menstruating endometrium constitutes a point of departure both for explaining the local and systemic phenomena related to menstruation, for investigating processes similarly preceded by withdrawal of estrogen and progesterone, and involving endometrial damage such as labor and the various types of pathologic pregnancy and for the study of other conditions in which injury of tissue is involved. Furthermore, it constitutes a basis for the development of treatment not only of disturbances associated with the premenstrual, menstruating, and pregnant uterus, but also of pathologic states resulting from many other varieties of tissue damage.

O. W. Smith has shown that the atypical euglobulin derived from the endometrium during its late stages of retrogression is experimentally a powerful tissue-damaging agent, capable also of inducing endocrine changes indicative of increased secretion and release of gonadotropic as well as adrenotropic hormone. She has also shown by immunologic studies, which require further investigation and confirmation, that this menstrual toxin and Menkin's canine necrosin are probably identical, thereby bringing into close relationship tissue damage in two species and from different causes. She has demonstrated fibrinolytic activity to be closely associated with menstrual toxin and canine necrosin, and has found fibrinolysin in the circulating blood during menstruation, labor, and toxemia of pregnancy, and following surgery and also in human pleural and peritoneal exudates. Furthermore, she has discovered that the pseudoglobulin fractions of all these fibrinolysin-containing fluids, with the exception of the circulating blood following surgery, which she has not yet tested, have the property of prolonging the survival time, and even occasionally of saving the lives, of immature rats given minimal lethal doses of menstrual toxin. This property requires painstaking, controlled experiments for its demonstration. Concentration of the pseudoglobulins is necessary. Protection appears to be a matter of quantitatively neutralizing the toxin and not of antibody formation in the ordinary immunologic sense.

I. Menstrual Toxin and the Local and Systemic Phenomena Related to Menstruation

The many and varied symptoms associated with menstruation and the other intangible concomitants of the process, such as changes in behavior, efficiency, etc., need not here be recounted. Suffice it to state that they all

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muscularly into four patients with primary dysmenorrhea, one of these patients having received it at the start of three different periods. Although relief or prevention of cramps seemed to result if the material was given within two hours of the start of flow, no conclusions can, of course, be drawn as to its clinical value on the basis of this subjective evidence.

Of more immediate significance were the studies of circulating fibrinolysin in three of these patients, namely, a reduction of the enzyme two hours after injection of the pseudoglobulin and its absence when the serum was tested eighteen hours later. One patient's serum was tested fifty-two hours later and again showed fibrinolytic activity. These tests were all run during the first three days of menstruation, at which time we have always found fibrinolytic activity in the serum of untreated women. Three of these patients volunteered the information that their flowing was more profuse than usual, an effect consistent with vascular and myometrial relaxation from partial neutralization of the toxin. The findings in these preliminary therapeutic trials constitute further circumstantial evidence in support of the concept that essentially all the menstrual phenomena do stem from the endometrium and are manifestations of local and systemic effects of the toxin. Moreover, the presence of the protective pseudoglobulin in the circulation during the catamenia is significant, since fluids in which toxin is found also contain this substance.

Our inability to demonstrate circulating toxin by tests with immature rats we attribute to the small quantities present. When larger volumes of serum are fractionated, the tests for toxicity become confusing because of nonspecific effects from the injection of larger amounts of protein. At this point one wonders why the protective pseudoglobulin already in the circulation during menstruation does not neutralize the toxin and reduce the fibrinolysin. We are at a loss to explain this paradox, unless we assume that the protective effect is the result of processing the serum. Protection with the serum of menstruating women is demonstrable only after removal of the euglobulin fraction. We have thought that this was due to the necessity of removing the fibrinolytic enzyme and toxin, but the possibility remains that some change in serum protein is effected which produces the protective factor. Even if this is the explanation, the precursors of this factor are apparently associated with the enzyme and toxin, since pseudoglobulin fractions of materials lacking in these properties are also lacking in protective action.

If the protective pseudoglobulin can be prepared in sufficient, concentrated amounts, we anticipate the prevention or amelioration of the disturbing and disabling concomitants of menstruation, chiefly irritation of nerves, as manifested most markedly in patients with epilepsy, and the irritation of smooth muscle which gives primary dysmenorrhea. The treatment of premenstrual tension is, on the whole, already satisfactory, but we are planning to try the protective pseudoglobulin in this disorder to test our idea that it is due for the most part to absorption of toxin. A crucial experiment would be the actual prevention of endometrial bleeding by the protective pseudoglobulin. In one patient, on two different occasions, the onset of flow appeared to be delayed by the injections when her period was due and she was having

reflect constitutional as well as local disturbance of greater or lesser degree. This conclusion is confirmed by the objective findings, both local and systemic, such as: uterine congestion, uterine contraction—even tetanic contraction, pelvic congestion, systemic retention of water, increased fragility of skin capillaries, exaggeration of dermatologic lesions, congestion of mucous membranes, changes in intestinal activity, exaggeration of cerebrospinal disorders, and changes as in the encephalogram. The pathologic physiology of these tangible concomitants of menstruation seems best explained on the basis of mild vascular insult resulting in congestion and stasis and mild damage, i.e., irritation, of other tissues as expressed by changes in the activity of muscles, mucous membranes, nerves, and skin. In other words, the pathologic physiology may be considered similar to that which takes place in the endometrium prior to the stage of vascular rupture and tissue necrosis. From the information already available, we are postulating that all the signs and symptoms related to menstruation are ascribable to the action of the menstrual toxin, with the possible exception of some engorgement and soreness of the breasts. The most obvious confirmation of this hypothesis lies in the repeated clinical observation that women with nonpathologic ovaries and without any endometrium have no symptoms indicative of ovarian hormone withdrawal except that some complain of periodic or aperiodic soreness of the breasts. It remains to be proved that these women with ovaries and without endometrium have none of the objective signs of ovarian hormone withdrawal just enumerated, but Thorn and Emerson,¹ in a careful study of water balance in one such patient, found one sign absent, namely, the retention of water consequent upon the drop of urinary estrogen.

Once shedding of the endometrium is under way, diuresis occurs and the menstrual molimina usually disappear or become milder, due, we think, to removal of the source of the toxin. In further support of our hypothesis is the usual absence of menstrual molimina in patients flowing from a proliferative endometrium, and in their endometrium and discharge O. W. Smith has found less toxin.

There is one more objective systemic finding that deserves mention, though its significance is still unknown, namely, a drop of serum diastase during the forty-eight hours before menstruation.² On the basis of circumstantial evidence, we have guessed that this might reflect increased activity of the adrenal cortex, a reaction which, according to our findings, would be expected to result from menstrual toxin.

We think that the amount and duration of endometrial bleeding depend on the amount and rate of formation of the toxin and whether it is formed focally or diffusely, these variables depending, in turn, upon hormonal balance and vascular behavior. The exaggeration of menstrual molimina termed premenstrual tension we would attribute to prolonged absorption of the toxin from a secretory endometrium before its disintegration. The spasm of primary dysmenorrhea we think is an exaggerated local effect of the toxin. To test this assumption we have thus far injected the protective pseudoglobulin intra-

TABLE I. PROTECTIVE PS TO PRE-ECLAMPTIC PATIENTS—EFFECT ON TOXIC SIGNS AND SERUM FIBRINOLYTIC ENZYME

| PATIENT | BEFORE R STARTED* | | | ADMINISTRATION OF PROTECTIVE PS. | RESULT | | |
|---|--------------------------|----------------------|------------------------------|--|-----------------------------|----------------------|--|
| | BLOOD PRESSURE AT 8 A.M. | ALBUMIN GRAMS IN 24° | FIBRINO- LYTIC† ENZYME | | BLOOD PRESSURE AT 8 A.M. | ALBUMIN GRAMS IN 24° | FIBRINO- LYTIC† ENZYME |
| Mrs. J. K. aged 30 para I gr. II | 150/100 | 1.9 | C | 2 × daily for 4 days | 115/70 | 0.7 | 0 |
| Mrs. E. H. aged 25 para I gr. I | 150/105 | 8.0 | C | then none for 6 days 2 × daily for 4 days | 150/90 120/85 | 1.8 3.2 | C 0.5 (0 in spec. after i.v.) |
| Mrs. E. B. aged 22 para I gr. II | 150/100 | 5.5 | C | 2 × daily for 6 days then none for 4 days then 2 × daily for 3 days | 128/85 140/95 130/85 | 2.1 5.2 3.2 | 0 C 0.3 |
| Mrs. F. L. aged 23 para I gr. I | 120/85 | 2.0 | 0.8 | 2 × daily for 6 days then none for 5 days then 2 × daily for 2 days | 120/60 140/100 120/80 | 0.8 2.9 1.3 | 0.4 C 0.6 |
| Mrs. R. S. aged 23 para I gr. II | 170/120 | 1.2 | C | 2 × daily for 6 days after 2 days after 6 days | 145/110 210/130 | 0.5 4.0 | - C |
| Mrs. B. M. aged 25 para I gr. II | 150/100 | 23.5 | 0.6 | 2 × daily for 6 days after 2 days after 6 days then 4 × daily for 1 day | 125/80 150/105 150/90 | 7.5 12.5 8.0 | 0 0.4 0 |

*All patients (except in Case 6) had been on routine hospital toxemic regime for one to three weeks before treatment with PPs.

†Degree of dissolution of standard fibrin clot after incubation for twenty-four hours with euglobulin fraction of 5 c.c. of serum. C = complete. The figures represent the proportion of the total 1 c.c. volume dissolved at twenty-four hours.

molimina. Perhaps if injections were continued in sufficient amounts the endometrium would regress without desquamation. The results of such an experiment would undoubtedly yield definite information concerning the purpose of menstruation. On the basis of the laboratory work and the endocrine findings just before and during menstruation, we can think of one possibly justifiable purpose, namely, toxic stimulation of the hypophysis. Because of this we have postulated that the induction of postovulatory-like endometrial bleeding in patients with anovulatory disorders might, through the action of the toxin, result in better gonadotropic activity. This is perhaps one reason why the use of progesterone in larger and properly-timed amounts, with the ensuing menstrual-like bleeding, has been an advance in the treatment of anovulatory disorders. It seems significant also that patients given progesterone-induced flowing from a secretory endometrium often complain of uterine cramps.

From the facts already available, however, the menstrual toxin probably affects all the tissues of the body so that some broader purpose than just toxic stimulation of the hypophysis needs to be found. The menstrual phenomenon may reasonably be considered to fulfil the requirements of an "alarm" reaction and a "general adaptation syndrome"³ and as such to keep the vegetative systems of the body "in line," as it were, for reproduction. This explanation still leaves unanswered why menstruation should be necessary in the female primate. We can only suggest that her vegetative systems would otherwise function improperly as a result of the increased cerebration presumed to occur because of her increased bulk of cerebral tissue.

II. The Termination of Normal Pregnancy

We have no positive evidence that a menstrual-like series of events plays any part in labor and delivery, but there are suggestive analogies between these episodes. Roughly, between the twenty-first and the second days before the onset of labor, when there is progressive withdrawal of the placental steroid hormones, retention of water takes place. Serum diastase decreases during the ten days before parturition, as it does before menstruation.² From studies thus far undertaken, Dr. Arthur T. Hertig has found evidence of retrogressive changes in the decidua in relation to delivery, for example, leucocytic infiltration. The circulating fibrinolysin and protective pseudoglobulin present after some hours of labor constitute another analogy to menstruation, although we are puzzled by the fact that these properties are not demonstrable at the start of spontaneous labor, especially since they appear in the circulation some hours before the onset of menstruation. We are likewise unable to explain by analogy why diuresis begins before labor, whereas it coincides with menstruation. We are, therefore, still hazy concerning the possible clinical significance of menstrual toxin in relation to the onset of labor, although the hormonal changes are entirely similar to those before and during menstruation and the development of toxemia of pregnancy, and in both of these situations there is good evidence of circulating toxin as a result of the withdrawal of hormonal support. The finding of circulating fibrinolysin and protective

Although it could be argued that the drops in blood pressure resulted from injecting changed protein and that the decreases in albuminuria were attributable to reduced pressure, a number of observations are against this explanation. In the first place the quantitative tests during the control period showed increasing albuminuria prior to injections, despite the fact that in all the patients hypertension had been considerably reduced by routine clinical measures. Furthermore, the effect of injections upon albuminuria was very much more striking than upon the hypertension. Finally, if the results observed were merely due to administration of changed protein, it is unlikely that the observed losses in weight would have ensued, and even more unlikely that the fibrinolysin would have disappeared or become diminished. Because of this possibility, however, O. W. Smith treated one patient for one day with a preparation of pseudoglobulin which she had found to be inactive in protection tests. At the end of the twenty-four hour period, the patient's urinary albumin and blood pressure had risen and her serum still caused complete dissolution of a fibrin clot. Then an active preparation was used and the desired changes followed.

The results of these preliminary therapeutic trials seem to us best explained as effects of neutralizing a toxic protein by another protein derived from damaged tissues. That they were obtained with a protein shown to be protective against the menstrual toxin appears to confirm our hypothesis that menstrual toxin is the cause of toxemia of pregnancy. Considering the sources of the protective pseudoglobulin, however, and the evidence for the similarity of menstrual toxin and a protein of widely different origin, namely, canine necrosin, and the association of fibrinolytic activity with other conditions involving damage of tissues (and this is not a new observation, dissolution of incubated clotted blood having for years been noted in cases of severe sepsis, toxemia of pregnancy and shock from various causes), we feel that the significance of these clinical tests is broader, that toxic protein catabolites from damaged tissues in general and menstrual toxin may be identical* and that therapy with the sort of pseudoglobulin now under trial may have far-reaching possibilities. This feeling is consonant with the present increasing realization of the importance of protein in the maintenance of homeostasis.

References

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*Dierks,⁴ for example, reported his studies of the endometrium and vaginal mucosa of a young woman dying of burns. The last menstrual period had begun fifteen days before death. Surface hyperemia and beginning coagulation necrosis characterized the late proliferative endometrium and the vaginal mucosa he interpreted as showing a picture typical of menstruation, namely, hyperemia and desquamation of the superficial layer.

pseudoglobulin after prolonged labor and following induced labor indicates that the toxin has been active. Furthermore, the well-known increased susceptibility of women at the time of delivery to shock from loss of blood and operative procedures and the occurrence of intra- and postpartum eclampsia are in keeping with the idea that a toxin is present. The occurrence of postpartum eclampsia would seem to point clearly to the decidua as its cause. We would theorize that the menstrual toxin does cause the prepartum retention of water and contribute to labor contractions through irritating the myometrium, but that something prevents fibrinolytic activity from manifesting itself in the circulation before and at the start of this event.

III. Toxemia of Pregnancy

O. W. Smith has described the finding of fibrinolysin and protective pseudoglobulin in patients with toxemia of pregnancy. A similarity to menstruation is also indicated by the following: the well-known retention of water, the withdrawal of estrogen and progesterone that precedes the disease, the decrease of serum diastase that preliminary studies² have shown to precede the disease, the increased uterine irritability, the systemic pathology which is like that of the premenstrual and early menstruating endometrium and, finally, the amelioration of the disease when the uterus is emptied and removal of decidua is under way. The fibrinolytic property of the blood of these patients disappears post partum. Therefore, we think that menstrual toxin is the precipitating cause of toxemia as well as menstruation. The presence of menstrual toxin in pre-eclampsia and eclampsia, however, remains to be proved, even though the circumstantial evidence for it is strong. Biological studies of the decidua, the blood coming away with the placenta and the lochial discharge remain to be performed. Whether or not the idea is new, we opine that toxemia of pregnancy is a disease peculiar to the human female because she menstruates, toxic separation of the placenta being the most striking example. Furthermore, we lean to the thought that once damage to systemic tissues by the menstrual toxin has progressed sufficiently, they themselves may release toxic protein and irreversibly aggravate the disease, making it similar to secondary or irreversible shock.

With the cooperation of the Boston Lying-in Hospital, O. W. Smith has thus far studied six patients with pre-eclampsia before, during, and after treatment with the protective pseudoglobulin made by her. The findings are shown in the accompanying table. All but the last patient had been in the hospital on toxic regime for one to three weeks before the trial of therapy. In addition to the decreases of blood pressure and urinary protein and the disappearance or diminution of the circulating fibrinolysin, losses of one to five pounds in weight were effected. When treatment was omitted, the findings were reversed. When treatment was resumed the reductions again followed. Although the complete disappearance of urinary protein was not brought about with the limited amounts of pseudoglobulin available, 50 to 68 per cent decreases were achieved.

tum. In the same year Gaines and MacDowell¹³ recorded still another fatality due to ruptured rectum. The first series was that of Kassebohm and Schreiber⁷ in 1937, consisting of 18 patients including the two deaths earlier reported. Borde¹⁴ in the same year published a monograph on the obstetric complications of lymphopathia venereum which included two postpartum deaths due to peritonitis (Cases 2a and 2b, Table I).

In 1938 Anderson¹⁵ described a death due to ruptured uterus following version and extraction. Pollard and Hellendahl¹⁶ in 1942 reported another fatality, due to ruptured rectum after breech delivery. In the same year Wilson and Hesseltine presented their series of 18 cases, including two cesarean sections, two patients with colostomy, and the first instance of delivery complicated by twins.

A series of 48 deliveries, including one death due to spontaneous intra-partum rupture of the uterus, was reported by Kaiser in 1943. He urged that cesarean section be reserved for those patients with extensive involvement of the pouch of Douglas or the pelvic soft parts. Spontaneous delivery and close postpartum observation were recommended in the event pelvic delivery was decided upon. In the same year Marciano¹⁷ reported 14 cases from Venezuela, including three cesarean sections and one maternal death. The latter patient was delivered by version and extraction after unsuccessful attempts at forceps delivery. She went into shock immediately post partum and parenteral therapy was given. However, the pulse disappeared, the patient suffered "*trastornos nerviosos*" (convulsions?) and expired in collapse. No autopsy is reported, but it seems likely that this patient died of hemorrhage due to a ruptured uterus. In 1944 Finn described 7 more cases, one of whom had a colostomy. Another of his patients suffered a ruptured uterus after four hours of labor and was successfully treated by section and hysterectomy. The maternal death recently referred to by Gusberg²⁰ has been previously reported by Pollard and Hellendahl.¹⁶

The first record of a patient delivered in the presence of a colostomy performed because of rectal stricture is that of Huet and Gauthier-Villars¹⁸ in 1935 (later reported again by Vignes,¹⁹ to whom Kaiser erroneously attributed this case). In 1942 Pollard and Hellendahl reported the first cesarean section done in the presence of a colostomy.

Reports of other isolated cases are included in Table I.

Experience at Charity Hospital

Thirty-eight deliveries productive of thirty-nine infants in twenty-six patients suffering from pelvic lymphopathia venereum have been found in the records of Charity Hospital in New Orleans for a period from 1937 to 1946. There were no maternal deaths. These cases are summarized in Table II.

At the time of delivery the parity of the patients was:

- Para 0—6 cases
- Para i—8 cases
- Para ii—7 cases
- Para iii—5 cases
- Para iv—5 cases
- Para v—3 cases
- Para vi or more—4 cases

Nineteen patients, or 70 per cent of the group, have had but one delivery under our observation after the diagnosis of rectal stricture was established. Four patients have had two deliveries, two patients three, and one patient four deliveries. No individual is known to have had an exacerbation of the lymphopathia in association with pregnancy.

LYMPHOPATHIA VENEREUM COMPLICATING LABOR

An Analysis of Thirty-Eight Cases

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LYMPHOPATHIA venereum complicates pregnancy primarily by the inflammatory lesions it produces in the mother which impede the progress of labor. The dystocia produced by this disease falls into two anatomic groups. The first is caused by the elephantiasis-esthiomene variety of vulvar lesions. Its management in no wise differs from that of similar soft tissue outlet dystocia due to other causes. The second type is caused by the extensive scarring of the soft tissues of the pelvis, of which the rectum is usually the first involved. This is due primarily to the virus and also to the usually associated secondary infection. The problems presented by this second type are unique in obstetrics.

Information concerning this subject continues to accumulate. Nevertheless the latest editions of standard obstetric textbooks (Beck,¹ Greenhill,² Stander³) and the larger systems of obstetrics and gynecology (Adair,⁴ Curtis,⁵ Davis⁶) provide incomplete information if they mention the subject at all. The most recent general review of lymphopathia venereum similarly fails to discuss the obstetrical complications adequately.²⁸

Only four series of cases of lymphopathia venereum complicating labor have been presented from American hospitals (Kassebohm and Schreiber,⁷ Wilson and Hesseltine,⁸ Kaiser,⁹ and Finn¹⁰). Of these, but two provide adequate data on a large enough number of patients (Wilson and Hesseltine—18 patients; Kaiser—48 patients) to permit conclusions as to the conduct of labor.

It therefore seems appropriate to present a series of 38 labors in 28 women with pelvic lymphopathia venereum observed at the Charity Hospital in New Orleans between 1937 and 1946. Further, it is proposed to discuss this complication and the problems directly related to it on the basis of the material available in the literature.

Review of Literature

One hundred twenty-four instances of rectal stricture complicating labor appear in the literature. Seventy-eight of these are included in Kaiser's report to which the reader is referred. An additional 46 cases omitted from that report are summarized in Table I.

The first recorded case of rectal stricture complicating labor was presented by Dorsett¹¹ in 1920. His patient died of peritonitis due to a rupture of the rectum following forceps delivery. Sixteen years later Kassebohm and Schreiber¹² reported two more deaths, one of them due to rupture of the rec-

TABLE II. THIRTY-EIGHT LABORS IN THE PRESENCE OF RECTAL STRICTURE OBSERVED AT CHARITY HOSPITAL

| PATIENT | AGE | PARTY | DURATION OF LABOR (HOURS) | TYPE OF DELIVERY | FETAL WEIGHT | PUERPERIUM | COMPLICATIONS |
|-----------|-----|-----------|---------------------------------|---------------------|-----------------|--------------|---|
| 1. L. T. | 38 | 4-3-1-0-3 | 12½ | Spontaneous | 6-7 | Afebrile | Colostomy Devine colostomy following a simple resection of rectum. |
| 2a. S. O. | 27 | -0- | 10 | Forceps | 5-10 | Afebrile | |
| 2b. S. O. | 30 | 1-1-0-0-1 | 20 | Forceps | 6-3 | Afebrile | Permanent loop colostomy established since last delivery. |
| 2c. S. O. | 31 | 2-2-0-0-2 | 4 | Forceps | 7-9 | Febrile | |
| 2d. S. O. | 33 | 3-3-0-0-3 | 3 | Spontaneous | 3 | Febrile | Devine colostomy. Vertex failed to descend after full dilatation. Pelvic examination revealed extensive scar- ring in adnexal regions. Tubal liga- tion at section. |
| 3. I. G. | 36 | 2-2-0-0-1 | 26 | Cesarean | 6-10 | Febrile | |
| 4. M. B. | 36 | 2-2-0-0-2 | 16 | Forceps | 6-13 | Afebrile | Abdomino-perineal resection and loop colostomy. Herniation of proximal loop two weeks from term responded to bed rest. |
| 5. N. E. | 35 | 1-1-0-0-1 | -- | Cesarean | 5-9 | Afebrile | Loop colostomy. Membranes ruptured prematurely and inductions of labor failed. Section followed by hyster- ectomy and bilateral salpingo-oopho- rectomy. |
| 6. A. F. | 35 | 5-0-1-1-0 | 18 | Cesarean | ? | Afebrile | Smith extraperitoneal operation done because of poor progress and pro- longed ruptured membranes as well as presence of stricture of rectum. |
| 7. C. B. | 25 | -0- | 17 | Forceps | 4-11 | Febrile | Marked scarring in pelvis noted. Sec- ond stage 6 hours. |
| 8. O. T. | 32 | 1-1-0-0-1 | ? | Forceps | ? | Endometritis | Prolonged labor of 2 or 3 days dura- tion with primary uterine inertia and intrapartum infection. Stillborn. |

TABLE I. FORTY-SIX ADDITIONAL LABORS IN THE PRESENCE OF RECTAL STRICTURE RECORDED IN THE LITERATURE

| AUTHOR | AGE | PARITY | DURATION OF LABOR | TYPE OF DELIVERY | FETAL WEIGHT | COMPLICATIONS |
|---------------------|-----|--------|----------------------|------------------------|-----------------|---|
| 1. Dick, W. | ? | ? | ? | Spontaneous? | ? | |
| 2. Borde, R. A. | 29 | ? | 20 | Spontaneous | 2,700 | Discharge of pus from anus at full dilatation. |
| 2a. <i>ibid.</i> | 28 | 0 | 48 | Forceps | 2,760 | Prolonged first stage. Maternal death in 24 hours due to peritonitis. Vagina, cervix and uterus intact. Incorrectly attributed to Vignes by Kaiser, Table I, Case 24. |
| 2b. <i>ibid.</i> | 32 | 0 | ? | Cesarean | 4,230 | Infant hydrocephalic. Maternal death due to peritonitis. Incorrectly attributed to Vignes by Kaiser, Table I, Case 23. |
| 3. Anderson, H. E. | 37 | 5 | 3½ | Spontaneous | 7-5 | |
| 4. Pollard et al. | ? | ? | ? | Cesarean | ? | Colostomy. |
| 5. Rodriguez et al. | 26 | ? | 15 | Spontaneous | 2,100 | Neonatal death. |
| 6. Goldman, H. | 30 | ? | — | Cesarean | 7-3 | |
| 7. Wilson et al. | 23 | 4 | ? | Cesarean | ? | Pelvic mass. |
| 8. Wilson et al. | 26 | 2 | ? | Cesarean | ? | Pelvic mass. |
| 9. Wilson et al. | 40 | 1 | ? | Forceps | ? | Rectovaginal fistula. |
| 10. Wilson et al. | 32 | 1 | ? | Spontaneous | ? | Twin delivery. |
| 11. Wilson et al. | 33 | 1 | ? | Spontaneous | ? | Colostomy. |
| 12. Wilson et al. | 23 | 0 | ? | Spontaneous | ? | } - Same patient. |
| 13. Wilson et al. | 25 | 1 | ? | Spontaneous | ? | |
| 14. Wilson et al. | 33 | 4 | ? | Spontaneous | ? | } - Same patient. |
| 15. Wilson et al. | 34 | 5 | ? | Spontaneous | ? | |
| 16. Wilson et al. | 26 | 4 | ? | Spontaneous | ? | |
| 17. Wilson et al. | 26 | 3 | ? | Spontaneous | ? | |
| 18. Wilson et al. | 24 | 0 | ? | Spontaneous | ? | |
| 19. Wilson et al. | 30 | 4 | ? | Spontaneous | ? | |
| 20. Wilson et al. | 30 | 0 | ? | Spontaneous | ? | Colostomy. |
| 21. Wilson et al. | 32 | 1 | ? | Spontaneous | ? | Rectovaginal fistula. |
| 22. Wilson et al. | 32 | 2 | ? | Spontaneous | ? | |
| 23. Wilson et al. | 37 | 1 | ? | Spontaneous | ? | |
| 24. Wilson et al. | ? | 2 | ? | Spontaneous | ? | |
| 25. Chavanne, F. C. | 35 | 4 | — | Cesarean | 2,450 | Rectovaginal fistula. |
| 26. Marciano, M. O. | 22 | 0 | 6 | Cesarean | 2,750 | Pelvic scarring noted. |
| 27. Marciano, M. O. | 21 | 0 | 9 | Cesarean | 3,540 | No cervical dilatation. |
| 28. Marciano, M. O. | 35 | 2 | — | Cesarean | 1,570 | Rectovaginal fistula. |
| 29. Marciano, M. O. | ? | 1 | 22½ | Version and extraction | 2,540 | Maternal death in shock, following unsuccessful forceps, attempted because of fetal distress in second stage, and then successful version and extraction. |
| 30. Marciano, M. O. | 42 | 0 | ? | Forceps | 2,900 | Artificial anus. 400 Gm. twin delivered. |
| 31. Marciano, M. O. | 28 | 6 | ? | Forceps | 3,500 | Vaginal scarring |
| 32. Marciano, M. O. | 27 | 0 | 17 | Spontaneous | 2,180 | Perineal fistulae. |
| 33. Marciano, M. O. | ? | 0 | 10½ | Spontaneous | 3,030 | Artificial anus. |
| 34. Marciano, M. O. | 25 | 3 | 5 | Spontaneous | 3,010 | |
| 35. Marciano, M. O. | 24 | 0 | 20 | Spontaneous | 2,400 | |
| 36. Marciano, M. O. | ? | 4 | 11 | Spontaneous | 3,510 | |
| 37. Marciano, M. O. | 42 | 11 | 4 | Spontaneous | 3,350 | |
| 38. Marciano, M. O. | 28 | 3 | 5½ | Spontaneous | 3,450 | Artificial anus. |
| 39. Marciano, M. O. | 30 | 1 | 17½ | Spontaneous | 3,270 | Perineal and genital lesions present. |
| 40. Finn, W. | ? | 4 | ? | Spontaneous | ? | |
| 41. Finn, W. | ? | 0 | ? | Spontaneous | ? | |
| 42. Finn, W. | ? | 2 | 6 | Spontaneous | ? | |
| 43. Finn, W. | ? | ? | ? | Forceps | ? | Colostomy. |
| 44. Finn, W. | ? | ? | ? | Midforceps | ? | |
| 45. Finn, W. | ? | 0 | ? | Forceps | ? | |
| 46. Finn, W. | ? | 6 | 4 | Cesarean | ? | Rupture of lower uterine segment after one hour second stage. Hysterectomy. |

Note: Fetal weight is given in pounds and ounces or grams as originally recorded by the author. "?" indicates that no information on this point is given in the original report. All presentations were by vertex.

Only two of the patients had contracted pelves, both of slight degree and of no clinical significance.

Five patients came to delivery, one of them on four occasions, with pre-existing colostomies. In two of these patients cesarean section was done. Three other patients had pre-existing rectovaginal fistulas, and another had had a rectal resection performed. There is little detailed information concerning the state of the strictures or the pelvic soft tissues. In many cases there were few spontaneous complaints referable to the bowels, and the rectal stricture was an incidental finding. Antepartum complications other than these were few in number.

At delivery thirty-two fetuses, or 82 per cent, were in normal vertex presentation and one was in breech. One presented by right mentum anterior. In five there is no record.

Method of delivery was as follows: spontaneously by vertex—twenty-three deliveries, or 59 per cent; forceps—ten, or 26 per cent; breech extraction—one; cesarean section—three, or 8 per cent; two not recorded. One twin delivery is included, both infants being delivered spontaneously by vertex.

Duration of total labor was not increased. There is no information available on the duration of the second stage of labor. Twenty-two labors, or 58 per cent, lasted under eleven hours, and seven more, or 18 per cent, lasted between twelve and eighteen hours. Only five labors lasted longer than eighteen hours. The most prolonged labor according to the records lasted fifty-five hours (Case 10a), but a review of the details makes it seem likely that about thirty-six hours of false labor are included in that figure. A secundipara (Case 8) suffered primary uterine inertia and intrapartum infection, but did well following forceps delivery. A grand multipara (Case 9) delivered a breech and twins without difficulty.

One patient (Case 2) delivered on four occasions in the presence of a colostomy, the latter two after a permanent loop colostomy had been established. The first three deliveries of term-sized infants were terminated by forceps, although labor in the last of these was of brief duration. Only the fourth delivery, a small premature weighing 3 pounds, terminated spontaneously. The mother recovered uneventfully each time.

Another patient (Case 3), a 36-year-old para 2-2-0-0-1* with a normal pelvis, was the most instructive one seen. She proceeded slowly but well in labor until full dilatation had been reached. Vaginal examination then disclosed membranes intact, vertex high, and cervix fully dilated. Extensive scar tissue involving the rectum, the rectovaginal septum, and all the soft tissues of the pelvis was palpated. The membranes were ruptured artificially, but despite good labor no further descent of the head occurred. Low cervical section and tubal ligation were carried out. At operation the rectum and lower sigmoid were found to be scarred, firm, and fixed to the sacrum. The entire posterior half of the soft tissues of the true pelvis were thickened and resistant, making clear that the failure of descent was due entirely to the infection of the soft tissues by lymphopathia venereum and its secondary effects. The patient had an uneventful convalescence. Had this patient been delivered by forceps or by version and extraction a tragedy would have been inevitable.

Two other cesarean sections were performed. A secundigravida (Case 5) failed to go into labor after premature rupture of the membranes despite several attempts at induction, and a section-hysterectomy was done. An essential primigravida (Case 6) also suffered premature rupture of the membranes and

*When parity is designated in this manner, the first number refers to the total number of pregnancies, the second to the full-term pregnancies, the third to premature deliveries, the fourth to abortions, and the last to the number of living children. In this example, the patient has been pregnant twice, had two full-term deliveries, no prematures, no abortions and one living child. She is a gravida iii, para ii.

| | | | | | | | |
|------------|----|-----------|-----|-------------------|------|---------------|--|
| 9a. C. C. | 30 | 8-6-2-0-6 | 5½ | Breech extraction | 7-7 | Afebrile | |
| 9b. C. C. | 31 | 9-7-2-0-7 | 8½ | Spontaneous twins | 4-8 | Afebrile | |
| 10a. M. A. | 27 | -0- | 55 | Forceps | 4-12 | Afebrile | |
| 10b. M. A. | 29 | 1-1-0-0-1 | 7 | Spontaneous | 5-9 | Afebrile | Rectovaginal fistula. Presentation by right mentum anterior. |
| 11. M. B. | 37 | 2-2-0-0-2 | 11 | ? | 7-2 | Afebrile | |
| 12. C. B. | 31 | 1-1-0-0-1 | 3½ | Forceps | 7-15 | Afebrile | Cause of sepsis not determined. |
| 13. A. B. | 35 | 1-1-0-0-1 | 16 | Forceps | 6-7 | One day fever | Rectovaginal fistula. |
| 14. V. B. | 38 | 3-3-0-0-3 | 8 | Spontaneous | 6-2 | Afebrile | Cause of sepsis not determined. |
| 15. E. D. | 29 | -0- | 12 | Spontaneous | 7-5 | Febrile | Cause not determined. Stillborn premature. |
| 16. E. H. | 29 | -0- | 31 | Spontaneous | ? | Febrile | Intrapartum infection. Stillborn. |
| 17. J. H. | 23 | 2-2-0-0-2 | 9 | Spontaneous | 9 | Afebrile | |
| 18a. A. H. | 31 | 3-3-0-0-3 | 9 | ? | 5-13 | Afebrile | Premature macerated stillborn. |
| 18b. A. H. | 33 | 4-3-1-0-3 | 5 | Spontaneous | ? | Afebrile | |
| 18c. A. H. | 34 | 5-4-1-0-4 | 12 | Spontaneous | 8-4 | Afebrile | |
| 19a. C. J. | 22 | 1-0-1-0-1 | 7 | Spontaneous | 7 | Afebrile | |
| 19b. C. J. | 26 | 2-1-1-0-2 | 5 | Spontaneous | 5-15 | Afebrile | |
| 20. H. P. | 35 | 4-4-0-0-4 | 5½ | Spontaneous | 6-4 | Afebrile | |
| 21. A. R. | 22 | -0- | 10 | Spontaneous | 7-10 | Afebrile | |
| 22a. C. S. | 27 | 3-3-0-0-3 | 6 | Spontaneous | 5-10 | Afebrile | |
| 22b. C. S. | 29 | 4-3-1-0-4 | 8½ | Spontaneous | 4-14 | Afebrile | |
| 22c. C. S. | 30 | 5-4-1-0-5 | 11½ | Spontaneous | 7-8 | Afebrile | |
| 23a. C. S. | 33 | 3-3-0-0-1 | 6½ | Forceps | 6-13 | Afebrile | |
| 23b. C. S. | 37 | 4-3-1-0-2 | 4 | Spontaneous | 4-8 | Febrile | Cause of sepsis not determined. |
| 24a. M. T. | 32 | 7-4-3-0-4 | ? | Spontaneous | 5 | Afebrile | Rectal resection done since last delivery. |
| 24b. M. T. | 38 | 8-5-3-0-5 | 5 | Spontaneous | 6-14 | Febrile | Pyelitis. |
| 25. O. W. | 36 | 1-1-0-0-1 | 9 | Spontaneous | ? | Afebrile | |
| 26. C. W. | 34 | 2-1-0-1-1 | 7 | Spontaneous | 6-15 | Afebrile | |

Note: Fetal weight is recorded in pounds and ounces. All presentations are by vertex unless otherwise noted. Each individual patient is assigned a number, and multiple deliveries in the same patient are designated by letter. ? indicates that no specific information on this point was found in the records.

ture. Three other operations were performed for multiple indications, including the lymphopathic process in two instances. Lymphopathia venereum was therefore implicated in at least two-thirds of the sections done, and in a section rate of at least 8 per cent in the whole series. Its etiologic connection is questionable in Finn's patient, in whom the section was done for ruptured uterus. The other sections were done for hydrocephalus, contracted pelvis, failure of labor with prolonged rupture of the membranes, and failure of the cervix to dilate. Marcano has suggested that this last condition is due to infection of the cervix by lymphopathia with secondary scarring.

Forceps delivery preceded three of the maternal deaths, a mortality rate of 12 per cent for the procedures. Inasmuch as study of the individual cases makes it likely that several of the uneventful forceps operations were performed as elective prophylactic procedures, the mortality rate for indicated forceps is undoubtedly much higher.

Following breech delivery, done in five instances, there was one death due to rupture of the rectum. The infant's weight is not recorded in this case report, and we can speculate only as to the role of the aftercoming head in producing this accident.

Version and extraction was performed four times, once for placenta previa in a multipara with a slight stricture and a 2,250 Gm. infant, and three times for dystocia. All three of the latter patients died, one of a ruptured rectum, one of a ruptured uterus, and one in shock with her reproductive tract intact. This leaves no doubt that version is absolutely contraindicated in the presence of pelvic lymphopathia.

Spontaneous delivery occurred in 101 cases and eventuated in two deaths, one due to ruptured rectum, and the other due to ruptured uterus. Therefore, not even this form of delivery can be regarded as entirely free of risk.

The maternal mortality rate for these 162 cases is 6 per cent. In all likelihood this is exaggerated by the many reports which have been concerned with isolated fatalities. The six series of patients reported include 143 cases with four deaths, a maternal mortality rate of 2.8 per cent, which seems a more likely figure. It is noteworthy that antemortem diagnosis of rupture of the rectum has never been made in these cases. The results of treatment of rupture of the rectum due to trauma, consisting mainly of fluid replacement, chemotherapy, and colostomy to divert the fecal stream, are sufficiently good to warrant the hope that postpartum patients would respond well to such treatment. The diagnosis can be made on the basis of appearance of shock post partum, accompanied by severe lower abdominal pain. The signs of peritonitis appear within a few hours. In its early stages, the condition may be confused with rupture of the uterus which itself necessitates laparotomy. A preoperative differential diagnosis might be made by an x-ray taken in the lateral decubitus position for the demonstration of air in the peritoneal cavity, although it has not been attempted in these cases. The *sine qua non* of diagnosis is a high index of suspicion when the presence of pelvic lymphopathia in the parturient is known.

made very poor progress when she finally fell into labor. In view of her age and the presence of the rectal stricture, an extraperitoneal section was performed. The results in these cases were excellent.

The puerperia in these thirty-eight deliveries were uneventful. Ten patients, or 26 per cent, had a febrile course, none of any gravity. There were no complications referable to the bowel complaints.

Two patients were sterilized, both at section.

The infants were not remarkable as to weight. Thirty-five, or 90 per cent, were living at birth. Two were stillborn following prolonged labors, and two more were stillborn prematures.

Discussion

There are now available for study 162 cases of labor in patients with rectal strictures and pelvic lymphopathia venereum. This study suggests certain rules for the conduct of labor in these patients, rules which have been previously discussed in part by several authors.

At this point a few comments on the incidence of this complication are in order. Finn¹⁰ states that "lymphopathia venereum is an obstetrical rarity," and is echoed in the latest edition of Stander's textbook.³ It is true that the disease is seen only rarely among white women in the United States, but it is not uncommon among Negro women. The series now reported from Harlem Hospital in New York,⁷ the Johns Hopkins Hospital in Baltimore,⁹ and the present series from New Orleans are sufficient to dispel any idea of actual rarity. Further, experience has shown that the incidence rises sharply when the members of the obstetric staff become interested in the complication, probably because under ordinary circumstances minor degrees of pelvic scarring are not likely to draw attention. From the data at hand it is not possible to make any reliable statement of the incidence of pelvic lymphopathia in gravidas. However, between 1937 and 1942, forty-two instances of this complication were seen at Charity and Hopkins Hospitals.

Since the finding of rectal stricture at once suggests the possibility of dystocia, we have summarized these 162 cases by mode of delivery in Table III.

TABLE III. MODE OF DELIVERY AND DEATHS IN 162 DELIVERIES IN THE PRESENCE OF PELVIC LYMPHOPATHIA VENEREUM

| MODE OF DELIVERY | NUMBER | PER CENT | DEATHS | | |
|------------------------|--------|----------|--------|-----------------------|---------------------------------------|
| | | | NUMBER | PER CENT OF 162 CASES | PER CENT OF CASES BY MODE OF DELIVERY |
| Spontaneous | 104 | 64 | 2 | 1.2 | 2 |
| Forceps | 25 | 15 | 3 | 1.8 | 12 |
| Cesarean section | 20 | 12 | 1 | 0.6 | 5 |
| Breech extraction | 5 | 3 | 1 | 0.6 | 20 |
| Version and extraction | 4 | 3 | 3 | 1.8 | 75 |
| Miscellaneous | 4 | 3 | 0 | — | — |
| Totals | 162 | 100 | 10 | 6.1 | |

Of the 20 sections performed, the indications for the operation are noted in the reports of eighteen. Eleven of these sections were done because of dystocia, either anticipated or actual, due to pelvic scarring and rectal stric-

soft tissues are so extensively involved as to preclude the passage of the presenting part, an elective section must be performed. The extent of the involvement may be judged in terms of fixation of the region of the pouch of Douglas, of adnexal thickening, and of the presence or absence of fistula formation. In most instances a trial of labor can be allowed, with the expectation that failure of descent of the presenting part will be followed by cesarean section rather than forceps or version, regardless of the state of dilatation of the cervix. Forceps should not be employed in patients with pelvic lymphopathia if the vertex is not at the outlet, unless failure to descend is exclusively due to some other obstetrical complication.

The presence of colostomy apparently does not present any special difficulties. One of our patients suffered a mild herniation of her colostomy about two weeks from term. This condition responded rapidly to bed rest and local care. Seventeen deliveries have been recorded in mothers with colostomies, without a maternal death, although presumably they suffered the most extensive disease of the group. It may be that diversion of the fecal stream allows resolution of some of the secondary infection and scarring. Three patients with colostomy delivered by section, seven by forceps, and seven spontaneously. For section, the area of the colostomy is simply draped out of the operating field. No wound infection due to contamination has occurred. Kaiser reported one colostomy and one precolostomy done at the time of section, with excellent results.

Postpartum care of patients with pelvic lymphopathia must be most meticulous for the first twenty-four hours, inasmuch as rupture of the uterus or rectum should be readily remediable if diagnosed. Heavy sedation should be avoided and the patient regularly and frequently examined. Peritoneal irritation or shock should immediately suggest rupture of the uterus or rectum, and indicate exploratory laparotomy.

Summary

Thirty-eight labors in the presence of pelvic lymphopathia venereum and rectal stricture observed in the Charity Hospital in New Orleans have been reported. There were no maternal deaths. Three cesarean sections were performed.

The 162 labors now recorded in the literature have a maternal mortality rate of 6 per cent, but this figure appears to exaggerate the actual risk. Force in delivery has played a large role in the reported fatalities. Version and extraction is absolutely contraindicated. Death is usually due to rupture of the rectum or uterus, either of which may occur with spontaneous delivery.

If soft tissue scarring due to lymphopathia venereum is widespread in the pelvis, the patient should be delivered by cesarean section. A trial of labor may be permitted, but if the presenting part fails to descend to the outlet, cesarean section rather than any form of pelvic delivery should be performed, regardless of the dilatation of the cervix. If the patient delivers per vaginam she should be watched diligently for signs and symptoms of rupture of the

Review of the deaths discloses that five were due to rupture of the rectum, two to rupture of the uterus, and one to peritonitis following cesarean section for dystocia in the presence of intrapartum infection. In addition, three women died early post partum, and autopsy was not obtained. Two of these deaths appear to be due to rupture of the rectum (Kassebohm and Schreiber¹² and Borde¹⁴) and one to rupture of the uterus (Marcano.¹⁷) There is no striking correlation of death with age, fetal weight, or parity. In two of the fatal cases of ruptured uterus, dystocia due to lymphopathia played a role by occasioning version and extraction. In seven of the deaths there is a record of forceful obstetric intervention by operators who were evidently unaware of the risks they faced. The death from peritonitis following section in an infected patient might have been avoided by an extraperitoneal approach, or, at the present time, by intensive chemotherapy.

There remains no doubt that forceful delivery must be avoided in any patient with pelvic lymphopathia who shows evidence of dystocia. The clinical criteria to be employed in obstetric management must be based on the pathologic anatomy of the disease. In this regard we cannot agree with Eastman's²⁵ statement that:

"Most important is the status of the rectovaginal septum. If this is involved in scar tissue, the elasticity of the vaginal wall is impaired, and tearing of the fibrosed vagina and attached rectum is likely."

Were this to occur, it should result in rectovaginal fistula or tears of the vagina, neither of which has been reported. In fact, the descent of the presenting part is impeded by scarring which is widespread in the pelvis. It is generally agreed that the virus of lymphopathia venereum spreads from the vulva by lymphatics to the perirectal lymph nodes and thence to the iliacs, leaving smouldering primary and secondary inflammatory changes in its wake. These produce the rectal stricture. In the patient with a severe or chronic case, the infection proceeds by retrograde spread in the bases of the broad ligaments and out laterally into the soft tissues of the pelvic wall. That labor is impeded by this cicatrized and unyielding mass was demonstrated classically in Case 3 of the series presented.

The rectum ruptures because its pelvic portion which is fixed to the vagina is torn away from the portion above the pouch of Douglas where it is adherent to the sacrum by scar tissue. The etiology of uterine rupture is not so clear. Two such ruptures followed version operations and were probably due to a combination of this procedure and the resistance offered by the soft tissues. Two uterine ruptures occurred spontaneously in multiparas and may simply have been coincidental. On the other hand, they may represent tearing of a lower uterine segment weakened by uterine contractions working against unyielding pelvic soft tissues.

The criteria for accouchement must be established with the condition of the soft tissues of the pelvis in mind. Presence of a rectal stricture will lead to further study of the patient, but it constitutes only a part of the anatomic picture. Examination is best performed under anesthesia. If, near term, the

LYMPHOGRANULOMA VENEREUM IN OBSTETRICS

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LYMPHOGRANULOMA venereum is a virus disease which produces a small primary lesion and systemic manifestations in its early stages, and localizes its later stages in the genitals and lower bowel. Two distinct syndromes may be produced, and either of these may cause obstetric complications of the utmost gravity.

Incidence.—Lymphogranuloma venereum is a rare disease in general, and is even more rare in association with pregnancy. At the Presbyterian Hospital in New York the diagnosis of this disease was made in 126 cases over a period of fifteen years. With some 280,000 admissions during this time, a general incidence of 0.045 per cent is produced. On the Obstetrical Service (The Sloane Hospital for Women) there were eight cases among 22,500 admissions over the same period, an incidence of 0.036 per cent. These eight cases are included in the grand total of 126.

There were, in all, 75 women and 51 men; and the 75 women comprise the material of this study. In this group 68 patients were Negroes (including the eight obstetric patients) and seven white, a distribution which supports the impression that lymphogranuloma venereum is primarily a disease of the Negro race. The disease was associated with one or more of the other venereal diseases (syphilis, gonorrhea, and chaneroid) in 39 of the 75 patients.

Relation to Fertility.—Whether lymphogranuloma venereum reduces the capacity of a woman to conceive and bear children is not clear at present. It has been demonstrated by Wilson and Hesseltine,¹ in a small group, that no impairment of the reproductive function is produced. The group reported in the present study demonstrates quite the opposite.

There were 45 patients in this group who became pregnant *before* the disease developed. The remaining 30 never became pregnant. No patient conceived for the first time *after* the disease appeared. Of the 45 women who became pregnant *before* the onset of the disease, only nine became pregnant again *after* the onset of the disease.

Among the 45 cases, 92 pregnancies occurring *before* the onset of the disease resulted in 62 living children, 3 stillbirths, and 27 abortions; while 17 pregnancies occurring *after* the onset of the disease resulted in 7 living children, 2 stillbirths, 8 spontaneous abortions, and one therapeutic abortion.

These figures suggest a definite impairment of fertility by the disease. In order to examine this possibility more closely, the influence of age was determined. There were 11 patients in the group which had borne children who

uterus or rectum. The appearance of peritoneal irritation or shock should suggest exploratory laparotomy.

Colostomy presents no special obstetric problems other than those found in other patients with pelvic lymphopathia venereum.

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McLane forceps were applied but delivery could not be effected. Version and extraction were then done, with episiotomy, and delivery was easy except for the head. This offered much difficulty, and was finally delivered very suddenly. The child was born alive. The patient went into partial shock, reacted once, and then died five and one-half hours after delivery. At post mortem there was a stricture of the entire rectum beginning 2 cm. above the anus. At a point 8.4 cm. above the anus was a laceration of the anterior and lateral aspect of the rectum opening directly into the peritoneal cavity. There was fecal fluid in the pelvic peritoneum and the pelvis. No Frei test had been done.

In 1937 Kassebohm and Schreiber reported 18 cases of rectal stricture in patients at term or in labor. Fifteen cases were delivered spontaneously with one death, a mortality of 6 per cent. Three operative deliveries occurred with one death, a mortality of 33 per cent. Autopsy on one of these deaths revealed a rupture of the rectum. In 1939 Vignes⁶ reported a case of rectal stricture with positive Frei test in which there was narrowing of the superior portion of the vagina and elephantiasis of the labia majora. A labor of sixty-two hours was terminated by a forceps operation made very difficult by the induration of the vagina, and death occurred thirteen hours post partum with symptoms of peritonitis. No autopsy was done, but it was ascertained that there was no rupture of the uterus and no cervical laceration. The origin of the peritonitis was thought to be a rupture of the rectum.

In a second case seen at the Sloane Hospital, lymphogranuloma venereum with an acute flare-up of the disease in the sigmoid and rectum constituted the complication to pregnancy:

E. H., a 36-year-old Negro multipara, was admitted to the Antepartum Clinic in May of 1941, at which time she was two months pregnant. She had had a known rectal stricture and proctitis for six years, with no change under treatment. In November, 1938, a cesarean section had been done at the Sloane Hospital for Women because of the stricture. At the time she appeared in this next pregnancy (May, 1941), termination of the pregnancy was advised but the patient refused it. She remained relatively well for three months, but on Aug. 31, 1941, she was seized with sudden lower abdominal pain, diarrhea, distention, vomiting, and a fever of 103° F. The pain localized to the left lower quadrant, and the diarrhea produced as much as 4 liters of foul feces per day. The colon became enormously dilated and the uterus was pushed to the right. There was no improvement with sulfaguanidine. Opiates gave partial relief. On the eleventh day of the acute episode she passed feces per vaginam with some decrease in pain and distention. On the eighteenth day she began to pass increasing amounts of pus by rectum, and a steady improvement in her general condition began. The fever disappeared during the next month. On November 30, she went into labor one month before her expected date of delivery. A cesarean section and hysterectomy were done, and a small but otherwise normal child of 1,950 Gm. was obtained. The postoperative course was uneventful.

The third was a patient with a long-standing stricture who developed complete intestinal obstruction during pregnancy:

M. P., a Negro para iv, gravida v had had a perirectal abscess at the age of 10 years. At 18 years of age, when pregnant for the first time, she had repeated perirectal abscesses and fistulas, and a diagnosis of rectal stricture was made. The Wassermann was four plus. A normal spontaneous delivery fol-

were 40 or more years of age at the time the diagnosis of lymphogranuloma venereum was made. When this group of 11 is excepted, there remain 34 cases potentially fertile at the time the disease appeared. Nine of these patients became pregnant again, with the results described above.

Relation to Obstetrics.—In the late stages, lymphogranuloma venereum causes two pathologic syndromes of obstetric significance. These are: (1) the ano-rectal syndrome, and (2) the genital syndrome or esthiomene.

In a space of five months, there appeared at the Sloane Hospital for Women three cases of the ano-rectal syndrome, each producing a different complication of the pregnancy. The first of these was a case of rupture of a rectal stricture which terminated fatally. This case, described in detail by Pollard and Hellen-dall,² may be summarized as follows:

J. T., 33 years of age, Negro, was admitted in labor at 2:40 A.M. on May 9, 1941. She had been treated as an outpatient for four years, and had a known rectal stricture. There was no proctitis. Her pelvis was gynecoid. The fetus presented as a breech, and shortly after admission the fetal heart became slow and irregular. A vaginal examination at this time disclosed a pulsating loop of cord prolapsed through a firm one-finger cervix. The patient was placed in Trendelenburg position, and the cord was replaced with much difficulty. Following this the fetal heart improved, and a No. 3 Voorhees bag was inserted. One hour later the fetal heart disappeared. She continued in labor for twelve hours, at the end of which time both feet and a loop of cord presented at the vulva. An easy breech extraction of a slightly macerated fetus was carried out.

The reaction to delivery was good, and one hour post partum she had a blood pressure of 100/78, pulse 88, temperature 100° F., and respirations 20. During the next eight hours there appeared increasing abdominal pain, tenderness, and distention. The pulse and respirations rose. The abdomen became stony hard; bloody fluid was passed by rectum; and twenty-one hours post partum the patient became suddenly comatose and died.

At autopsy there was found a complete tranverse rupture of the rectum, at a point 8 cm. above the anus. The ends of the rectum were 10 cm. apart. The lower 8 cm. of the rectum was markedly stenotic, with a lumen of 0.5 cm., and it was tightly bound down. The rupture occurred in the uppermost portion of this stricture. Above the rupture was a portion of normal colon 7 cm. long containing impacted feces, and above this was a second stricture 3.5 cm. long. There was marked generalized fibrinopurulent peritonitis.

There have been four similar cases previously described. In 1920 Dorsett³ described a case of a 37-year-old patient who had had three previous deliveries without complications. She was delivered at home by low forceps. Almost immediately she had pain in the left side, very shortly went into shock, and died in forty-two hours. She had a known rectal stricture which was said to be syphilitic, the Frei test not having been described at that time. At autopsy there was found a rupture of the rectum at the rectosigmoid junction in the upper extremity of the stricture, and an acute diffuse peritonitis. In 1936 Gaines and McDowell⁴ described the case of a 19-year-old white primipara with a history of "rectal trouble" for several years, who was seen for the first time in active labor for twenty hours. She had a very tight rectal stricture beginning just within the anus and extending as far as the finger could reach. Tucker-

Discussion

The described cases, and those reported in the literature, demonstrate that lymphogranuloma venereum which has progressed to its late stages produces a serious complication in the pregnant patient. It would further appear that, in this series, the presence of the disease also diminishes the fertility of the patient.

When conception does occur in a patient with rectal or genital involvement, there may result a normal pregnancy and a spontaneous delivery. But in other cases, and it is impossible to predict which ones these will be, there may occur a flare-up of the disease during the pregnancy, or the rectal involvement may proceed to the point of complete intestinal obstruction. Because of these possibilities, it would seem wise to advise against pregnancy in a patient with active disease or with a rectal stricture, and termination should be considered if pregnancy has occurred in such a patient.

The chief danger which exists at the time of delivery is that of rupture of the rectum. In the reported cases this has always resulted in death, and this accident has been associated with an operative procedure in all but one case. This means that vaginal delivery of a patient with a rectal stricture exposes her to the possibility of irreparable damage. It is true that a number of patients have been delivered uneventfully from below, and this number is greater than the number of those who have died. But with the risk so great, it would seem wiser to deliver all patients with rectal strictures or the genital syndrome by cesarean section. Where this cannot be done, the delivery may be allowed to take place from below if operative interference is kept to a minimum, and when interference cannot be avoided the manipulations should be as gentle as possible.

Summary

1. The incidence of lymphogranuloma venereum has been recorded, with particular reference to obstetrics.
2. Impairment of fertility by the disease has been demonstrated.
3. The gravity of the possible complications warrants advising against pregnancy in a patient with active disease or a rectal stricture, and warrants consideration of termination if pregnancy has occurred.
4. In patients with rectal stricture or esthiomene the method of choice for delivery is by cesarean section.
5. If delivery must be allowed to take place from below, manipulation should be carried out only when it is unavoidable.

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lowed, and there was a second at 20 years of age. At 22 years, with proctitis continuing, delivery at term was obstructed by a circular band of scar tissue beneath the vaginal mucosa just within the introitus. This band gave way during a midforceps delivery, but the mucosa remained intact. The next year the rectal stricture was divided but it recurred. At 24 years another normal delivery occurred. In the next 8 years there were continuing proctitis and intermittent inguinal swellings, together with occasional systemic symptoms.

In 1941, at 32 years of age, she became pregnant again. Constipation, lower abdominal pain, and proctitis increased until at seventeen weeks gestation complete intestinal obstruction developed. This was only partially relieved by a Miller-Abbott tube and colon lavages, and at eighteen weeks the pregnancy was terminated by supravaginal hysterectomy. The postoperative course, with tube in place for six days and then without tube, was remarkably free of distention. Two months later she felt quite well and was having daily bowel movements without pus or blood, although the stricture was quite narrow.

Esthiomene

The late syndrome of esthiomene or elephantiasis has also produced a number of cases of dystocia. Cohen, in 1930,⁶ reported a case of ulceration of the vulva with elephantiasis which caused great difficulty in extracting the aftercoming head. He quotes a case of Tschnewski in which perforation of the aftercoming head was necessary under similar circumstances. Riviers and Boursier⁶ had to resort to cesarean section after a trial of labor in a case of marked elephantiasis of the labia minora and clitoris in which the vaginal introitus was constricted and indurated, especially over the perineum. Delivery was done by cesarean section after a trial of labor had been given.

Delivery From Below

Labor is not always obstructed and complications are not the invariable rule in cases of lymphogranuloma venereum. At the Sloane Hospital there have been four full-term deliveries and one premature normal delivery in cases of rectal stricture. Of the 18 cases reported by Kassebohm and Schreiber, 15 patients were delivered spontaneously and three operatively. In the 16 cases which survived, the morbidity was 50 per cent, but there were no other complications. Wilson and Hesseltine reported 18 patients with a total of 58 pregnancies, 21 of which were observed. These resulted in 19 living children and 3 abortions (two therapeutic). The deliveries were carried out by cesarean section in two cases, once for extensive sloughing of the vagina and once for a large pelvic mass. One patient was delivered uneventfully by low forceps, and the remaining 16 had nonoperative deliveries. Two of these had permanent colostomies because of severe strictures. A third, a case of twins had a fecal impaction above a stricture. The stricture was dilated during labor and the impaction removed by repeated enemas, after which engagement and delivery occurred. Huet and Gauthier-Villars⁶ had a case of severe proctitis due to lymphogranuloma which required a colostomy. Two normal deliveries occurred despite continuing disease which completely obliterated the rectum. Anderson⁸ reported a patient with marked proctitis and large stricture, together with elephantiasis of the labia majora. This patient had three quick normal deliveries despite the stricture. Michelson⁹ and Dick¹⁰ each had a case of stricture with a normal delivery.

California Hospital and 286 Rh-negative private patients from the private practice of one of the staff members of that hospital.* The control series consists of 1,129 pregnancies occurring in 237 Rh-positive mothers from the same clinic and 297 Rh-positive mothers from the same private practice. All the Rh-negative patients obtainable from both sources were used, and a comparable number of Rh-positive patients were selected from both sources by a purely alphabetical random choice. Exclusion of patients from the series was done only on the basis of incompleteness of data. Cases included were studied from 1944 to the present.

Inasmuch as data on the Rh status of husbands were incomplete, Rh-negative mothers with Rh-negative husbands have been included in the series. The number of cases is great enough, however, so that we may safely assume for the Rh-negative group of mothers approximately an 85 per cent incidence of "Rh-incompatible" matings. Data on the Rh status of the delivered infants were, for various reasons, equally incomplete, so no attempt is made to present them.

Rh determinations on all patients were carried out in the laboratory of the Sub-Division of Preventive Medicine of the University of California Medical School. The patient's own statement regarding the outcomes of previous pregnancies was accepted whenever it was deemed reasonably dependable. If there was doubt whether an early termination of pregnancy represented an abortion or premature delivery of a viable infant, that pregnancy was excluded from the series. ("Viable" is here used in the sense of duration of pregnancy greater than five lunar months.) Any error present in the series on this account is equally present in the control series.

A certain degree of error arises, however, from the tendency of many patients to conceal a history of previous induced abortion, such a termination of pregnancy often being reported as a spontaneous one. For this reason no attempt has been made in this series to separate spontaneous from induced abortions. Indeed, the "abortion rate" quoted in the tables represents *all* interruptions of pregnancy prior to the fifth lunar month. The incidence of mole, therapeutic abortion, and the like, is extremely small, however; and here again the equal and large sizes of the two series makes it possible to draw valid conclusions from a comparison of them.

Material is also presented to arrive at the abortion rate in the pregnancies of mothers who at any time during their childbearing careers bore an infant which manifested hemolytic disease of the newborn. The criteria used for the diagnosis of this condition are those previously discussed by Overstreet and co-workers.⁹ They have been adhered to in both the private and the clinic series of cases. Since the latter two series are essentially identical in size, handling of patients, criteria for diagnosis, number of patients, and serological study, their analytical treatment as a single series is justified and leads to more mathematically significant conclusions. It may be added in passing that a separate statistical analysis of the private and clinic cases shows only an increased sampling error with no findings at variance with those of both series treated as a unit.

Findings

Table I presents the total abortion rate for 1,129 pregnancies in Rh-positive mothers, 15.2 per cent, as compared with that of 1,038 pregnancies in Rh-negative mothers, 12.4 per cent. The difference in rate, *opposite* to what one would expect if Rh-isoimmunization played a part in causing early abortion, is explainable only on the basis of sampling error.

Table I also presents the abortion rate for primigravid pregnancies and for multigravid pregnancies in the Rh-negative and the control series. It has

*We are greatly indebted to Dr. Ernest W. Page for the opportunity to include in this analysis the data obtained from private patients.

DOES RH-ISOIMMUNIZATION CAUSE EARLY ABORTION?*

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IN 1942 Levine¹ suggested that maternal isoimmunization by fetal Rh antigen might play an etiologic role in spontaneous early abortion. He stated that "clinically it was already known that mothers of erythroblastotic infants have a higher than normal incidence of spontaneous abortion," and he illustrated this statement by presenting the outcomes of 37 pregnancies in 7 Rh-negative mothers, 6 of whom showed anti-Rh serum agglutinins. Ten of these pregnancies aborted, giving an abortion rate of 27 per cent—considerably higher than normal expectation.

Since Levine's report, and coincident with the recent intensified interest in the role of Rh-isoimmunization in pregnancy, it has been generally assumed that a considerable number of early abortions could be attributed to this mechanism. Many authors,²⁻⁶ in discussing either the over-all problem of abortion or the clinical aspects of the Rh factor in pregnancy, have emphasized a supposed responsibility of the obstetrician in this regard. They have urged that cases of habitual abortion or even patients who have simply aborted a single pregnancy be subjected to immediate study of the Rh status of both marital partners in the hope of accounting for the abortion tendency.

Yet the medical literature offers no study which demonstrates conclusively that Rh-isoimmunization plays any part in causing early abortion. Indeed, some evidence to the contrary is available. Javert,⁷ from a study of 55 cases of erythroblastosis and 12 cases of habitual abortion, concluded that "unless additional evidence shows the contrary, early habitual abortions should not be attributed to isoimmunization." Hunt⁸ studied 25 cases of habitual abortion with reference to the Rh factor and concluded that "the Rh factor is not of great importance as a common cause of such untoward terminations of pregnancy."

In spite of such findings the opinion persists, even in the very recent literature, that Rh-isoimmunization probably plays a part in the causation of a certain number of early abortions—if not in the so-called habitual abortions, then at least in single or spaced abortions of Rh-negative mothers with Rh-positive husbands. It is our hope that the statistical evidence here presented may cast further light on this belief.

Clinical Material

An analysis is made of 1,038 pregnancies occurring in 226 Rh-negative mothers from the Division of Obstetrics and Gynecology of the University of

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†Assisted by a grant from the Columbia Foundation of San Francisco.

Both the over-all abortion rate, 14.1 per cent, and the rate for multigravid pregnancies, 17.8 per cent, are no higher than they are for the corresponding pregnancies in Rh-positive mothers, 15.2 per cent and 17.8 per cent, respectively. The extremely low rate for primigravid pregnancies of Rh-negative mothers is doubtless due to the small number of pregnancies and consequent large sampling error. In any event, in none of the pregnancies of this special group of Rh-negative mothers is the abortion rate apparently contributed to by the known capacity of their mothers for Rh antibody production.

Perhaps a more concrete approach to the question may be undertaken through an examination of the salvage of viable infants from the pregnancies of Rh-positive mothers, Rh-negative mothers, and Rh-negative mothers who have

TABLE III. RECOVERY OF VIABLE INFANTS FROM RH-NEGATIVE MOTHERS

| FROM | NUMBER OF PREGNANCIES | WHICH WERE | TYPE OF PREGNANCY | WERE OBTAINED | NUMBER OF VIABLE INFANTS |
|------|-----------------------|-------------------------|-------------------|----------------------------------|--------------------------|
| | 534 | Primigravid, Rh+ mother | | | 469 |
| | { 512 | Primigravid, Rh+ mother | | $(\frac{512}{534} \times 469 =)$ | 450 |
| | { 512 | Primigravid, Rh- mother | | | 456 |
| | 595 | Multigravid, Rh+ mother | | | 489 |
| | { 526 | Multigravid, Rh+ mother | | $(\frac{526}{595} \times 489 =)$ | 434 |
| | { 526 | Multigravid, Rh- mother | | | 453 |

TABLE IV. RECOVERY OF VIABLE INFANTS FROM RH-NEGATIVE MOTHERS WHO HAVE BORNE AT LEAST ONE CHILD WITH HEMOLYTIC DISEASE OF THE NEWBORN

| FROM | NUMBER OF PREGNANCIES | WHICH WERE | TYPE OF PREGNANCY | WERE OBTAINED | NUMBER OF VIABLE INFANTS |
|------|-----------------------|-------------------------|-------------------|---------------------------------|--------------------------|
| | 45 | Primigravid, Rh+ mother | | $(\frac{45}{534} \times 469 =)$ | 40 |
| | 45 | Primigravid, Rh- mother | | | 42 |
| | 90 | Multigravid, Rh+ mother | | $(\frac{90}{595} \times 489 =)$ | 74 |
| | 90 | Multigravid, Rh- mother | | | 74 |

borne erythroblastotic infants. These data are presented in Table III and Table IV. The expected salvage for a given number of Rh-negative mothers is simply calculated from the actual salvage obtained from the whole Rh-positive control series. It will be noted that in each instance the recovery of viable infants from the pregnancies of Rh-negative mothers was equal to or greater than the recovery from an equal number of pregnancies of Rh-positive mothers. We are, therefore, unable to adduce any statistical evidence that Rh-isoimmunization cuts down, by means of abortion, the number of viable infants one would expect to recover from a given number of pregnancies.

Discussion

Our general knowledge of the mechanism of Rh-isoimmunization in pregnancy has now become extensive enough so that we may, with some profit, consider theoretically its possibility as an etiologic factor in early abortion. Voluminous work has established the fact that fetal damage by Rh-isoimmunization does not occur in the absence of maternal production of Rh antibodies, either

been amply demonstrated that Rh-isoimmunization and the fetal damage it produces become more manifest in succeeding pregnancies. We should expect, then, that isoimmunization, if it played a part in early abortion, would produce in

TABLE I. ABORTION RATE IN RH-POSITIVE AND RH-NEGATIVE MOTHERS

| TYPE OF PREGNANCY | MOTHERS' Rh STATUS | ABORTION RATE |
|-----------------------------------|-----------------------|----------------|
| All pregnancies (2167) | Rh-positive (1129) | 15.2% (171) |
| | Rh-negative (1038) | 12.4% (129) |
| Primigravid pregnancies (1046) | Rh-positive (534) | 12.2% (65) |
| | Rh-negative (512) | 10.9% (56) |
| Multigravid pregnancies (1121) | Rh-positive (595) | 17.8% (106) |
| | Rh-negative (526) | 13.9% (73) |

multigravid pregnancies an abortion rate appreciably higher than that for the Rh-positive, multigravid controls. No evidence of this is manifest in our series. While the abortion rate rose from 12.2 per cent in the primigravid pregnancies of Rh-positive mothers to 17.8 per cent in the multigravid pregnancies of Rh-positive mothers, it rose only from 10.9 per cent in the primigravid pregnancies of Rh-negative mothers to 13.9 per cent in the multigravid pregnancies of Rh-negative mothers. Were it not for the fact that this difference in increase is certainly due to sampling error, one might even say that Rh negativity conferred a small degree of protection upon the multigravid pregnancies of Rh-negative mothers so far as abortion is concerned. There is, at any rate, no evidence that Rh-negativity contributes to the abortion rate of multigravid pregnancies any more than it does to that of primigravid pregnancies.

It is, however, in the pregnancies of the Rh-negative mother who has fully demonstrated her ability to form damaging antibodies—by bearing a child manifesting hemolytic disease—that we might expect to find the highest abortion rate of all. Whether it would appear in the primigravid pregnancies of such mothers is doubtful, but we surely might expect the multigravid pregnancies of a mother who had had one or more erythroblastotic infants to be subject to a high incidence of early interruption due to Rh-isoimmunization. The pregnancies of 45 such mothers are presented in Table II.

TABLE II. ABORTION RATE IN RH-NEGATIVE MOTHERS WHO HAVE BORNE AT LEAST ONE CHILD WITH HEMOLYTIC DISEASE OF THE NEWBORN

| TYPE OF PREGNANCY | MOTHERS' Rh STATUS | ABORTION RATE |
|-------------------------|-----------------------|----------------|
| All pregnancies | Rh-positive (1129) | 15.2% (171) |
| | Rh-negative (135) | 14.1% (19) |
| Primigravid pregnancies | Rh-positive (534) | 12.2% (65) |
| | Rh-negative (45) | 6.7% (3) |
| Multigravid pregnancies | Rh-positive (595) | 17.8% (106) |
| | Rh-negative (90) | 17.8% (16) |

stillbirth at eight months, with marked edema of the child. The fourth pregnancy, 1936, terminated in a stillbirth at seven months, with marked edema of the child. The fifth pregnancy, 1938, terminated in a stillbirth at six months, cause unknown.

One week before the last menstrual period associated with the present pregnancy the patient's blood showed a 1+ anti-Rh titer with partial blocking. Next titer taken in twelfth week of pregnancy showed 4+ anti-Rh. All subsequent titers have shown between 2+ and 4+ anti-Rh with partial blocking on two occasions. The patient at present is in the thirty-second week of pregnancy.

Here we have a patient who has had repeated loss of infants due to Rh-isoimmunization—five pregnancies with no living child. Yet all her pregnancies have reached a viable size. In the face of repeated maternal sensitization sufficient to produce premature delivery and stillbirth due to erythroblastosis no pregnancy has been spontaneously aborted. The maternal blood showed a 1+ anti-Rh titer even before the onset of pregnancy and a 4+ titer early in its course, yet the pregnancy is now in its thirty-second week and the patient has at no time presented any symptoms of threatening abortion. If Rh-isoimmunization played any role in the causation of abortion, it is almost inconceivable that this patient should not have aborted at least one of her pregnancies.

Summary and Conclusions

1. A statistical analysis of the outcomes of 1,038 pregnancies of 512 Rh-negative mothers as compared with those of 1,129 pregnancies of 534 Rh-positive mothers is presented. The abortion rates for all pregnancies of Rh-negative mothers, for primigravid or multigravid pregnancies of Rh-negative mothers, and for pregnancies of Rh-negative mothers who have borne at least one child manifesting hemolytic disease of the newborn are no higher than for the corresponding pregnancies of Rh-positive mothers. The salvage of viable infants from the pregnancies of Rh-negative mothers is equal to or slightly greater than that from the corresponding pregnancies of Rh-positive mothers.

2. Doubt is cast upon the assumption that Rh-isoimmunization is an etiologic factor in early abortion.

3. A theoretical explanation is offered to account for the findings.

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anti-Rh or blocking. Moreover, Page, Hunt, and Lucia¹⁰ have recently shown that maternal antibodies must be produced for a certain *period of time* before clinically appreciable fetal damage occurs. They have determined this period to be approximately ten weeks.

One must distinguish, of course, between fetal damage and placental damage. While it is possible that placental damage taking place earlier than fetal damage might account for early abortion due to Rh-isoimmunization, all our present knowledge indicates that such placental damage takes place concurrently with or somewhat later than fetal damage. Many cases of subclinical hemolytic disease of the newborn, for example, appear to have normal placentae so far as routine microscopic examination of placental sections is concerned.

It seems likely, therefore, that at least ten weeks of maternal sensitization must take place before the mechanism can play any part in the termination of pregnancy.

Our present knowledge does not include the stage of fetal development at which fetal red blood cells first show the presence of Rh antigen. Bornstein and Israel¹¹ were able to demonstrate its presence in the red cells of a non-macerated fetus 17 cm. in length, that is, at approximately four months duration of pregnancy. Earlier development of the antigen is likely, but specific evidence is lacking. While reasoning by analogy is dangerous, it should be pointed out that Kemp¹² was able to demonstrate only the probable presence of B agglutinin in a fetus thirty-seven days old, and at this age the agglutinin strength was very low. Should essentially the same be true of the Rh antigen, it may well be that the first two to four weeks of pregnancy are incapable of producing any isoimmunization.

If we may further assume—as would seem permissible from the data of Page, Hunt, and Lucia—that several weeks more than the ten-week period might be required to produce damage extensive enough to result in expulsion of the pregnancy, then the summation of the time factors alone would be in the neighborhood of twenty weeks, the onset of the period of viability.

The foregoing discussion is in no sense an attempt at theoretical disproof of the Rh-isoimmunization etiology of early abortion. It is simply offered as a possible explanation for the absence, in our series, of any statistical evidence for the existence of such an etiologic factor.

Moreover, now that serologic studies on the Rh factor in pregnancy have been carried out for a number of years, many of us have encountered individual cases whose circumstances argue strongly against Rh-isoimmunization as an abortifacient mechanism. The following patient is a case in point.

Mrs. V. L. is a 41-year-old gravida vi, para 0, with a negative Kahn and Kolmer whose last menstrual period began on July 8, 1946. There is no history of transfusion. The husband is Rh-positive. The first pregnancy, 1928, terminated in spontaneous birth of a 7-pound infant who received transfusion but died in twenty-four hours. The second pregnancy, 1930, terminated in a full-term stillbirth, cause unknown. The third pregnancy, 1933, terminated in a

STUDIES IN UTEROTUBAL INSUFFLATION*

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TRANSUTERINE insufflation of gas holds an established place as a clinical means of determining tubal patency in cases of human sterility. The application of kymographic recording methods to insufflation of both human beings and experimental animals has suggested many hypotheses of both academic and clinical import. Many of the conflicting deductions which have been advanced in the past are due to lack of suitable research instrumentation. This investigation was undertaken to determine the clinical value of uterotubal insufflation from two aspects:

1. Technique of insufflation and criteria of patency;
2. Significance and value of the kymographic tracing.

Determination of Patency by Insufflation

The physical principle behind the employment of insufflation for the determination of tubal patency is that the pressure in a gas-filled system depends upon the differential between the rate of gas inflow and the rate of gas escape. For clinical purposes, the ideal instrument should be one that can deliver the minimum quantity of a nontoxic gas at a constant, measurable slow rate of flow with a suitable manometer registering the pressure developed in the system.

Believing that manometric determinations alone are sufficient to indicate clinical patency, I do not await the confirmatory evidence gained by the introduction of 10 to 15 c.c. of gas, which is the minimum required to induce "shoulder pain" or be visible as a subphrenic collection to x-ray. Satisfactory determinations can be secured by the intraperitoneal insufflation of but 2 to 3 c.c. of gas. When such small amounts are used, the choice of gas becomes relatively unimportant. Carbon dioxide is employed largely for its theoretical advantages of low toxicity, high solubility, and easy procurement. Inert poorly soluble gases would probably produce less experimental error, and the danger of symptomatic air embolism becomes highly remote when small quantities are insufflated. Five cubic centimeters of atmospheric air have been frequently injected intravenously into rabbits without inducing convulsions or death, whereas the introduction of larger amounts is a common technique of sacrificing the animal. Although detailed protocols on all embolic case fatalities following clinical insufflation are not available, it is probable that considerably more than 5 c.c. of gas under pressure was introduced.

To meter the gas at a slow, measurable rate, Rubin's volumeter was replaced by a rotameter. The objections to the volumeter are manifold:

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Addenda

The subsequent course of this patient—after acceptance of this paper for publication—is of especial interest. It was determined that the sixth and present pregnancy was sired by a second husband, also Rh positive, while the first five had the first husband as father. The patient delivered spontaneously, three days past the estimated date of confinement, a living, Rh-positive, 3,080 Gm. child who manifested mild hemolytic disease of the newborn and required two transfusions. Postpartum serologic study of the maternal and fetal blood suggests, but does not prove, that isoimmunization during the sixth pregnancy was produced by an antigen of a different Rh subgroup than that responsible in the first five pregnancies. From the point of view of isoimmunization, then, the sixth pregnancy might correspond to a primigravid one.

Since submission of this material for publication, a paper by Hunt¹³ has presented a similar study of the incidence of abortion in 333 pregnancies of Rh-negative mothers. We are happy to add further statistical support to his conclusion that "casual or ordinary abortion seems uninfluenced by the mechanism of the Rh factor."

tubes are patent enough for the passage of a fertilized ovum. The diameter of the ovum at its discharge from the follicle is approximately 100 to 150 micra. If the outlet of the apparatus is reduced to this diameter, a flow rate of ten cubic centimeters of gas per minute develops no pressure within the system whereas at sixty centimeters per minute, a flat level of 10 mm. Hg of pressure is generated. Of course, these mechanical observations cannot be directly applied to consideration of transit of a fertilized ovum, but when the subject of mechanical stenosis is considered it presents us with the order of lumen diameters secured at particular pressures. With adequate control of physical factors in the apparatus and increasing experience in insufflation to detect leakage of gas at the cervix, it is possible to eliminate the confirmatory evidence of "shoulder pain" or pneumoperitoneum to x-ray. Insufflation is stopped when the manometer indicates that the pressure has fallen or remains stable for a few seconds, and patency of one tube can be considered present if this pressure level is below 100 mm. Hg. There is little virtue in testing patency at pressures higher than 150 mm. Hg. Rupture of a freshly ligated normal tube has been observed at a pressure of 140 mm. Hg. The use of high pressures to therapeutically "force a block" is more likely to rupture the tube than dilate a stricture.

If patency is not secured, insufflation is repeated at least six times consecutively, allowing several minutes of rest between each trial. In normals, the pressure at which gas enters the peritoneal cavity varies considerably. It has been shown² that on repeated insufflation at the same sitting, the gas enters the peritoneal cavity at progressively lower pressure levels. Normal patients may present "closed tubes" at one time, using all criteria including x-ray to be re-insufflated at later dates and demonstrate normal patency. Neurogenic and humoral factors unquestionably play a role.³ To eliminate "spasm," reassurance is frequently of more value than antispasmodic drugs. To establish the diagnosis of organically closed tubes requires failure to secure patency upon repeated insufflations. For these reasons, caution must be exercised before ascribing therapeutic benefits to either forced insufflation or other moduli of therapy merely because single observations revealed that the tubes were closed prior to treatment to be found open after therapy.

As would be mechanically expected, there would be a small group of cases wherein our manometric criteria would indicate closure, although the patient subsequently suffers "shoulder pain" or has roentgen evidence of subphrenic air. In the absence of defective valves permitting sudden surges of gas flow, these cases must be classified as "patent to some gas" but not patent enough for the passage of a fertilized ovum. This group would automatically disappear if only small quantities of gas are insufflated.

The Kymographic Tracing

Until recently, Rubin used two types of apparatus to record the fluctuations in pressure secured during continuous insufflation. One comprised an ink writer floating upon the column of mercury in the open manometer and the other, the Grafax model, has an ink-writing lever activated by an aneroid manometer. Both machines displayed considerable lag and required large volumes of gas for recording. On test, approximately 68 c.c. of gas were needed to drive the mercury recorder from the base line to a level indicating 200 mm. Hg., while 25 c.c. sufficed for the Grafax model. At a flow rate of 60 c.c./min., machine artifacts become considerable. In 1943, he mentioned but did not describe two modifications.⁴ In one, the volumeter was apparently eliminated, while pressure was recorded by the Grafax aneroid. In the other, recording was secured by

1. This device does not directly indicate flow rate at any particular instant. Operating on a siphon principle, wherein gas displaces water so that 25 to 40 c.c. of gas are delivered with each regurgitation, calibration is necessary prior to each test. This is time consuming and wasteful of gas. Introducing a shut-off valve distal to a fixed setting of the flow-regulating valve does not furnish an accurate solution because of the fluctuation in delivery of the best needle valves.

2. The gas enters the uterus after having been moistened by the unsterile water in the volumeter.

3. Evaporation of water from the volumeter requires frequent refilling. The rotameter consists of a small glass tube with a tapering lumen through which the passing gas floats an aluminum marker. This gauge is calibrated to produce a linear relation between the height of the marker and rate of gas flow.

For the gas to flow, it must enter the system at a head of pressure exceeding a working range of five pounds. A tank of gas under greater pressure will ensure flow, but the rate of flow cannot be kept truly constant. With a tank pressure of twenty pounds, a variation in flow of the order of twenty per cent may occur between rate of delivery of gas at atmospheric pressure and one against a resistance of 200 mm. Hg. This error can be reduced by admitting gas at a pressure higher than twenty pounds, but it has not been possible to secure adequate rotameter calibration or fine enough needle valves which would operate at high pressures. In the Rubin apparatus, the flow-controlling needle valve is proximal to the volumeter. To overcome this unmeasured resistance, the valve has been placed distal to the rotameter.

To record the pressure in the system, an aneroid or mercury manometer may be used. The former has the advantage of compactness and it requires less gas to produce a reading comparable to that secured by the mercury manometer.

The uterus is sounded to determine the direction of the canal and to rule out a stenosis of the cervix. A Keyes-Ullman cannula is introduced and, in most cases, satisfactory leak-proof obturation may be secured without counter-traction on the cervix with a tenaculum. For cases with markedly dilated cervical canals, the screw type of cannula is preferable.

The gas is introduced at a rate of 10 c.c. per minute, a rate much slower than the 60 c.c. recommended by Rubin. There are two factors serving to limit the rate of gas flow. At a minimum, it must exceed the rate of gas absorption through the intact uterine mucosa. In several cases with known tubal obstruction, carbon-dioxide was introduced to build up a pressure of 200 mm. Hg., and the time for absorption of the measured quantity of gas was determined. Absorption is at a rate slower than 0.1 c.c. per minute. The maximum rate of flow is conditioned by the rate at which the operator wishes the pressure to rise in the system. Gas frequently fails to pass through the tubes at pressures of 200 mm. Hg. at a rate of flow of 60 c.c./minute when it has entered at lower pressure levels when the rate of flow was reduced. The explanation for this phenomenon is not clear, but the rapid distention of the uterus at higher rates of flow may conceivably produce "reflex spasm" of a functional nature.

Rubin has introduced manometric criteria for patency based upon numerous human insufflations.¹ With normal patency, he estimated that 120 mm. Hg is the upper limit of pressure developed when rates of gas flow are of the order of sixty cubic centimeters per minute. At slower rates of flow, this manometric limit should be lower and is probably of the order of 80 to 100 mm. Hg. However, thousands of insufflations must be performed on normal, fertile women to learn, statistically, this true upper limit of pressure compatible with functional patency. Mere escape of gas into the peritoneal cavity does not imply that the

1. A primary rapid rise in pressure followed by an abrupt fall which is called the primary pressure peak.

2. A plateau of sustained pressure about which fluctuate major and minor waves of pressure. The major and minor waves differ in character as well as amplitude. The rate of climb of both types of waves and of the primary pressure peak parallels each other but is slower than that secured on simple mechanical obturation of gas escape from the apparatus. The rates of fall in pressure of the minor waves tends to be rapid and abrupt, and almost equals the rate of fall observed when the escape of gas is suddenly released from the system. The rate of fall of the major waves is distinctly slower.

A comparison of the tracings secured by the Grafax model, mercury float, and the strain gauge reveal surprisingly few differences. The strain gauge which is the most sensitive displayed no greater frequency of waves, but the amplitude of all waves tended to be much greater with falls almost or to the base line.

Four possibilities are present to explain the origin of these rhythmic waves of pressure. The fluctuations may be due to resistances produced by:

1. Contractions of the uterus with the tubes acting as passive agents.
2. Contractions of the tubes with the uterus completely quiescent.
3. Contractions of the tubes with the wave of contraction originating in the tube but sweeping over the uterus which contracts synchronously or shortly after the tube.
4. Independent, unrelated contractions of both tubes and uterus.

Categorically, the waves of pressure recorded by the mercury float or Grafax apparatus cannot be produced by uterine contractions with the tubes acting as passive, hoselike channels. Pressure changes recorded by these machines require such a large volume of gas that approximately 0.35 c.c. of gas must be displaced to register a wave of pressure of 1 mm. Hg. A cannula was introduced into the uterus of a rabbit so close to its uterotubal junction that the uterine cavity volume was reduced to a volume of less than 0.2 c.c. With a Grafax model, usual type of tracing was still obtained with waves of pressure of ten or more millimeters being recorded. The strain gauge will record pressure variations of 1 mm. with but 0.01 c.c. of gas displacement, but the frequency of waves obtained on experimental insufflation does not increase. Additional evidence was obtained⁵ by driving radiopaque fluid through the human uterus and tube and in these experiments, tubal contractions were always detected when the tracing exhibited a rise in pressure.

As to the second possibility, experiment indicates that the uterus is not completely quiescent during insufflation. On ligating the isthmie portion of the tube of a rabbit and distending the uterus with gas, pure uterine contractions can be elicited with the strain gauge at all levels of insufflating pressure, i.e., to 200 mm. Hg. In one of the illustrations in his recent article,⁴ Rubin demonstrated uterine contractions at levels of pressure similar to that of the plateau level observed during insufflation.

Reynolds⁶ has presented an admirable summary of the work of Westman and others upon direct observations of tubal and uterine contractions in several species, including the rabbit. To quote him, ". . . the motility of the uterus in oestrus is normally governed by the arrival of excitatory waves from the tubes . . . at times other than oestrus, the uterine threshold to excitation of neighboring areas of myometrium by contraction in either the tubes or in various

a "photo-electric" system. In 1942, Mayer and associates⁵ used an optical drum on the Wiggers principle with excellent sensitivity. The objection to this apparatus is the necessity of working in a darkened room and the difficulty of following pressure variations during the experiment.

To obviate these difficulties, a recording insufflator was constructed on the principle of the "strain gauge." Briefly described, the strain gauge operates on the principle that the resistance of a wire is affected by the mechanical strain induced in it. A suitable gauge was applied to the surface of a tiny copper-beryllium drum which in turn was joined by narrow brass piping to the

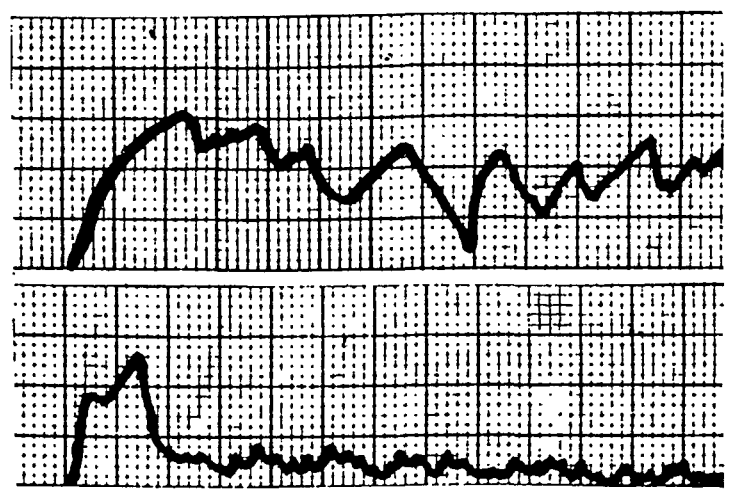
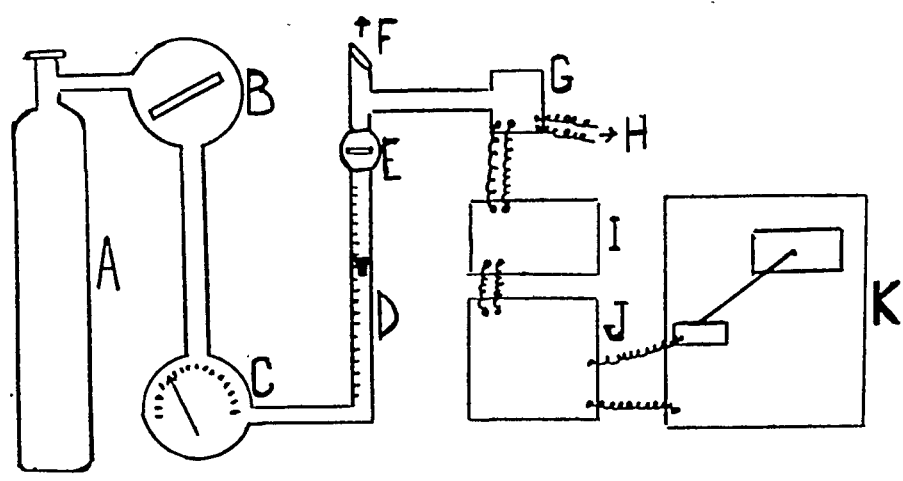


Fig. 1.—Schematic plan of apparatus and two typical tracings secured in normal women. A.—tank of gas under 600 pounds' pressure; B.—reducing valve; C.—gauge indicating pressure of gas delivery; D.—rotameter with float; E.—valve controlling rate of gas flow; F.—tube leading to patient; G.—strain gauge; H.—bridge voltage, 5 volts, 60 cycle A.C.; I.—carrier amplifier; J.—rectifier and filter; K.—direct writing oscillograph.

Rotameter. Changes in pressure within the system deformed the drum and induced strain in the gauge. With suitable rectification and amplification, a record of change in resistance and therefore of pressure was obtained by a direct writing oscillograph (Fig. 1). Under test rates of flow of 10 c.c. of gas per minute, thirty full swings of the recorder, registering a span of 200 mm. Hg., could be obtained, whereas barely two are obtainable under similar conditions with the Grafax model.

The tracings secured by all types of apparatus during insufflation of humans or animals present several features in common:

gested that seen in nerve activity rather than the variety induced by smooth muscle automatism. These bursts were always recorded over both the uterus and the tube (Fig. 4).

4. The animal was killed by the intravenous injection of 50 c.c. of air and reinsufflated. Only major types of pressure waves were observed without any of the minor waves. None of these waves were preceded by the bursts of electrical activity recorded above, and the tracing of the electromyogram resembled that of the nondistended uterus (Fig. 5).

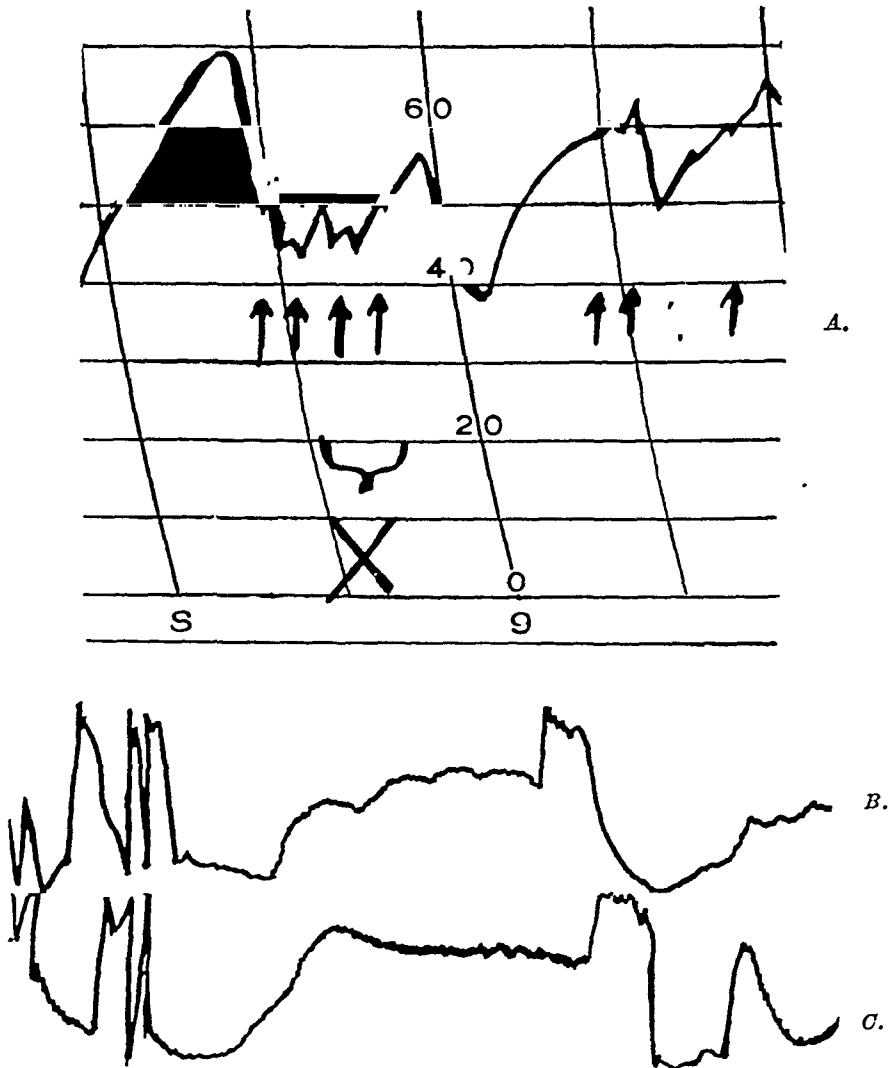


Fig. 4.—Insufflation tracing of same animal employed in Fig. 3, after eight minutes of insufflation with appearance of major and minor waves of pressure (A) and electromyographic tracing of tube (B) and uterus (C) during the period embraced by the bracket.

It is doubtful that the waves of pressure observed on insufflation are produced by unrelated independent contractions of the tube and uterus. In the intact animal, I have been unable to secure electromyographic evidence of uterine contractions sufficient to produce a wave of pressure to insufflation without similar electrical activity in the tube. Numerous observers have commented upon the higher frequency of automaticity of the tube compared to the uterus. Insufficient numbers of animals have been tested during pregnancy and in estrus

places of the uterus, is high, although the property of automatism persists and shows itself by weak activity in every part of the organ. . . ." An experiment was performed to confirm this third possibility, i.e., some of the waves of pressure observed on insufflation originate in contractions of the tube but that the contraction waves sweeps over the uterus as well. Bozler has described the uterine muscle of the rabbit as a syncytium.⁷ Under local anesthesia, a rabbit was insufflated according to the technique of Feresten and Wimpheimer⁸ with a Grafax recorder. The uterus and tube was drawn out of the abdomen to separate them from contact with adjacent viscera. A pair of electrodes were placed 3 mm. apart upon the midportion of the uterus, and another pair on the isthmus portion of the homologous tube. The electrodes were connected to a two-channel pen writing oscillograph adjusted to record 20 microvolts. The following observations were made:



Fig. 2.—Electromyographic tracings of nondistended tube (A) and uterus (B).

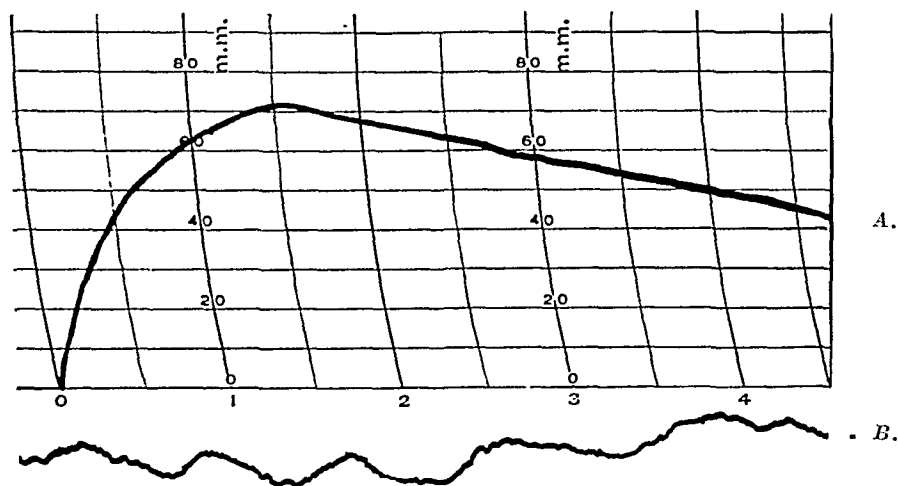


Fig. 3.—Insufflation tracing depicting normal primary peak and plateau with total absence of waves of pressure (A) and electromyographic tracing of tube (B).

1. Mild evidence of electrical activity was observed in the contracting non-distended uterus and tube (Fig. 2).

2. At the onset of insufflation, a primary pressure peak and plateau were obtained but the plateau, as is frequently seen, was flat without either major or minor pressure waves. The electromyogram during this period revealed little change from that in the nondistended uterus (Fig. 3).

3. After five minutes of continuous insufflation, both major and minor waves of pressure were recordable. Preceding each of the minor waves, tremendous electrical activity in the form of bursts were recorded, whereas the major waves were unaccompanied by any such changes. The type of electrical discharge sug-

I cannot confirm Rubin's claim that adhesions about the tube would produce disappearance of the waves of pressure.⁴ It is difficult to reconcile his claim that pins inserted into the seromuscular edge of an extirpated tube cause the rhythmic contractions to disappear with the work of Feresten and co-workers⁸ that all of the tube except for minute portions of the isthmus may be removed with little change in the tracing. I have confirmed Feresten's work on numerous occasions. Frequently, one secures an otherwise normal tracing except for absence of the waves of pressure in normal, fertile women or in animals, and if the insufflation is continued for as long as twenty minutes, normal types of waves reappear. Experience in uterine manometrics has shown that as much as fifteen minutes of continuous distention of the uterus may be necessary before uterine contractions become demonstrable. I have never clinically observed a wave-free otherwise normal tracing when insufflation was continued for twenty minutes except in menopausal, normal women. Even in these cases, prolonged insufflation beyond this period and possibly at higher pressures may elicit contractions, for even an atrophied uterus and tube retains some degree of automaticity inherent in smooth muscle.

Insufficient studies have been made to evaluate humoral effects upon the insufflation tracing. Hormonic studies with insufflation possesses no advantage over similar experimentation with the intrauterine balloon, but does retain the potential disadvantage that insufflation in the postovulatory period may hydraulically drive the ovum out of the uterus or tubes.

Summary

1. The technique and criteria for patency determined by uterotubal insufflation have been described, using an improved form of insufflation apparatus.

2. Kymography, of large academic interest, has furnished no additional information as to the pathologic state of the tubes.

The technical advice of Dr. Harold Lamport, Yale University School of Medicine, and Mr. Paul Traugott, Director of the Electro-Physical Laboratory, is gratefully acknowledged.

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and anestrus states, but it is doubtful that the uterus ever acts as the pacemaker for the tube. Certainly with the Grafax or mercury manometer types of recorders, all waves of pressure must be construed as purely tubal in origin. Further electromyographic study would be of interest in an analysis of the neurogenic factors involved.

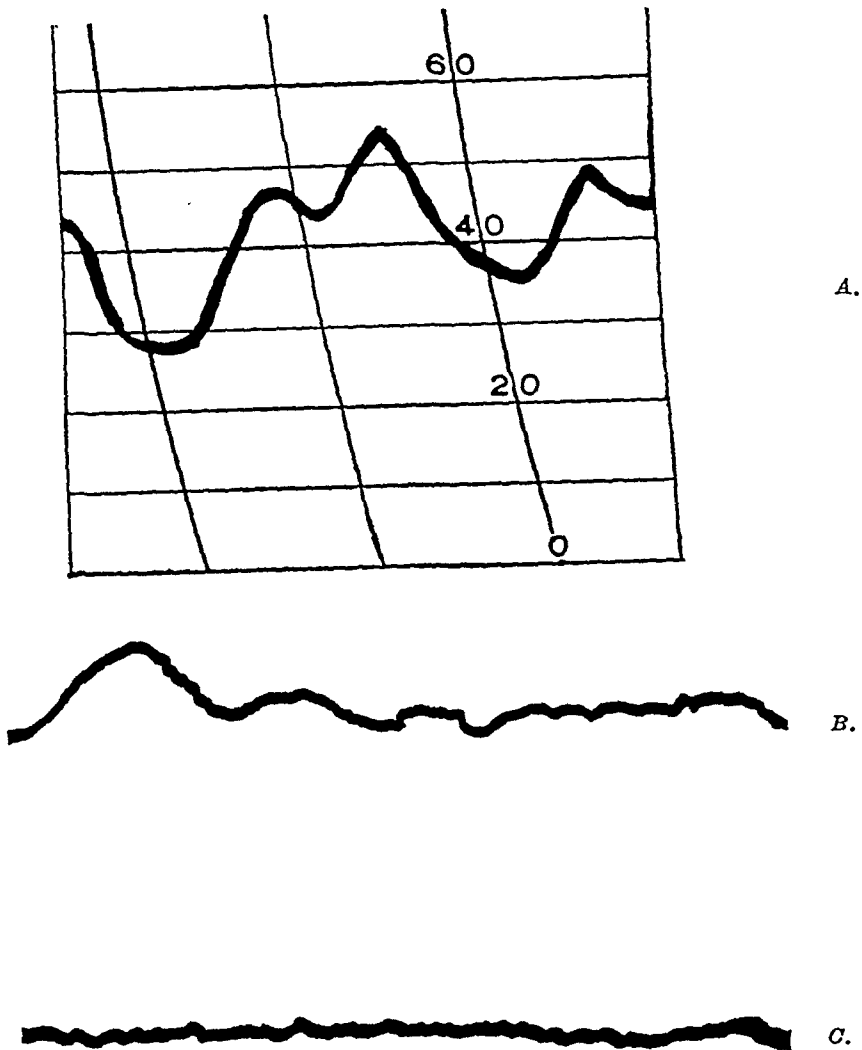


Fig. 5.—Insufflation of dead animal with tracing indicating only major waves of pressure (A) and electromyographic tracing of tube (B) and uterus (C) during this period of insufflation.

I share Rubin's contention that a study of the insufflation tracing may furnish evidence of a strictured tube. Mechanical considerations demand strict criteria for establishing the diagnosis of stricture of the tube. The primary pressure peak and plateau levels must persistently remain above the 100 or 150 mm. Hg level used as an index of patency; the same level or higher must be reduplicable upon repeat insufflation; the insufflation must be conducted long enough to rule out sustained partial "functional closure" or spasm. As a secondary phenomenon, the major and minor waves of pressure might be shallow or absent, for the amplitude of these waves is to some extent inversely proportionate to the plateau level.² I have never encountered a clinical case that satisfied these criteria.

was, therefore, 15.35 per cent. It was interesting to note that there was not a single infection to cause concern in this group. Also, there was only one case which hemorrhaged sufficiently to require emergency transfusion. So striking were these two features that the author has come to feel that any severe hemorrhage or severe infection in an abortion should be treated as an induced abortion.

Of the 937 who aborted, 356 were lost before studies were completed. A thorough preconceptional study was carried out on each of the remaining 581. This study and the management of the cases have improved in the light of newer knowledge and the discovery of newer medicine and biologicals. Out of this completed group, 520 or 89.5 per cent were carried through a successful pregnancy after the study. In the completed group there were 153 habitual aborters, which was 27.3 per cent of the group. Of these habitual aborters, 64.1 per cent were carried through to a period of viability, though many not to full term. This 64.1 per cent success, though far from the desired results, is certainly encouraging in the face of an outlook of about 27 per cent if not treated.

Among the 581 cases which were completed, there were 292, or 50.3 per cent, pregnancy test negative on admission. Most of those with positive tests were later found to have retrodisplaced uteri, infantile uteri, low prothrombin levels, and some low estrogen levels. This percentage of positive tests is quite low as compared with what might be expected if all cases were included who did not actually abort as these patients did. Practically all those with low pituitary function, low progesterone, or low estrogen-progesterone levels, and some low estrogen level cases were negative on admission. Undoubtedly, many women who have nidatory bleeding will go ahead and carry through without treatment.

TABLE I. INCIDENCE

| CONDITIONS | NO. CASES | PER CENT | REABORTERS | PER CENT |
|---------------------------|-----------|----------|------------|----------|
| Infantile uterus | 77 | 13.2 | 4 | 5.2 |
| Retrodisplaced uterus | 158 | 27.2 | 2 | 1.2 |
| Low prothrombin level | 19 | 3.2 | 0 | --- |
| Low estrogen effect | 168 | 28.9 | 0 | --- |
| Habitual aborters | | | | |
| Low pituitary effect | 37 | 6.3 | 2 | 5.4 |
| Low progesterone effect | 54 | 9.3 | 26 | 48.1 |
| Low estrogen-progesterone | 68 | 11.7 | 27 | 39.4 |

Table I lists the conditions which existed and were thought to have been responsible for the abortion in the completed group. The table also shows those who aborted again under preconceptional and continued treatment.

Thus, it can be seen that 442, or 72.7 per cent, were not habitual aborters. In this group all were carried through the next pregnancy with the exception of six cases for a 98.6 per cent success. The degree of success here seems quite high, but it must be remembered that this group is one in which a high percentage would carry through anyway, and the treatment is merely an aid. However, in the habitual abortion group it is felt that treatment has accomplished something worth while. It may be noted that the low pituitary group who are still able to become pregnant offer a very good prognosis under therapy, but usually a very poor one without it. The low progesterone group seems to offer the least hope.

Causative Factors

In the series here presented there were no abnormalities attributable to tumors, infections, or lacerations of the cervix. Neither did thyroid dysfunction alone seem to play a part, although the general well-being of the patient was improved if given when indicated. There were no abortions which could be directly traceable to alcohol, lead, diabetes, or incompatibility of the Rh factor.

ABORTIONS: A STUDY WITH EMPHASIS ON TREATMENT*†

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IT IS impossible at present to evaluate results on known viable fetuses at the time of beginning treatment. However, in these studies, an approach to this has been attained by employment of an Aschheim-Zondek or Friedman test on all threatened abortions. The urine was always collected before active treatment was begun. As will be noted from the results, a very high percentage of admissions were negative, denoting that the fetus had ceased to be viable some ten days to two weeks before abortion threatened. For purposes of drawing more accurate conclusions as to the effects of medication, all cases, including the pregnancy test negative cases, were treated the same way for each group, and no abortion was completed until passage of tissue had occurred.

For purposes of this study, abortion refers to the expulsion of the fertilized ovum any time before a good state of viability is attained, or around the thirtieth week. This is an attempt to remedy those cases which abort, and no obvious cause is detected at the time.

In general, opinions seem to fall into three divisions: (1) abnormalities of the ovum, (2) abnormalities in the maternal developmental environment, and (3) paternal abnormalities.

Having seen only one fetal abnormality in those cases later carried to fetal viability who did threaten to abort under care, leads this author to agree with Mall and Corner that such abnormalities are on an environmental basis.

Malpas concluded that after two successive abortions 62 per cent would have a normal pregnancy; after three, 27 per cent; while after four only 6 per cent, without any specific treatment.

Author's Series

This study has been carried out over a ten-year period, from June 30, 1936, to July 1, 1946, during which time there were 6,105 viable babies and 937 spontaneous abortions under the writer's observation on various Naval Maternity Services to which he was assigned. Approximately 5 per cent of the births were repeats in the same patients. The 937 tabulated abortions represent different persons. This group comprised 235, or 25 per cent of the total, who had aborted three or more times and were classed as "habitual aborters." The others were largely primi-aborters which accounted for 665 or 71.1 per cent of the total, while the second aborters accounted for only 37, or 3.9 per cent of the total. The incidence of abortion in the total 7,042 pregnancies

*Data from the Obstetrical and Gynecological Departments of various U. S. Naval Hospitals. The author is now Head of the Department of Obstetrics and Gynecology, and Officer in Charge of Dependents' Service, U. S. Naval Hospital, National Naval Medical Center, Bethesda, Maryland.

†The opinions and/or assertions contained herein are the private ones of the writer, and are not to be construed as official or reflecting the views of the Navy Department or the Naval Service at large.

if one is to obtain best results, the patient must be thoroughly studied when she is not pregnant, and then be advised to become pregnant at the optimum time.

It has been the author's practice to give each patient who has previously aborted a thorough study, including a good history, basal metabolic rates, glucose tolerance studies, Rh factor studies, etc. The physical examination alone will reveal such defects as infantile uterus, or retrodisplacements of the uterus. A prothrombin level is taken on all patients, preferably during a menstrual period. Also, any pregnant woman who bleeds has a prothrombin level estimation made. Since earlier studies the author has ceased to make checks on the vitamin C levels. The low prothrombin level patients complain of general sluggishness and weakness. This same feeling of poor well-being is found in low pituitary function cases, but is readily relieved by a 20 per cent protein diet, whereas the low prothrombin level patients are not.

A history of frontal headaches which are noted usually upon arising and wearing away with the day, and edema before menses or in the previous pregnancy are indicative of low estrogen level. A history of failure to be nauseated is indicative of less than average gonadotrophic factor.

Endometrial biopsies are taken for study of the endometrium along with vaginal smears. These can be checked with estrogen and pregnandiol determinations on the urine also, but is not practical as yet, and was used in very few cases in this study.

These studies have shown that from biopsies and vaginal smears one may determine estrogen and progesterone effect with a fair degree of accuracy; sufficiently so for practical purposes. This, however, is not the whole story, since the cause in each case may be different. Glucose tolerance and glucose-adrenal tolerance curves will aid in determining if the pituitary function is low. There is also the feeling of generalized weakness and lassitude. There is an increasingly low basal metabolic rate. These findings along with biopsies and vaginal smears indicating low estrogen-progesterone effect will give a diagnosis of low pituitary function as the primary factor. Also, in early pregnancy these cases show low serum gonadotrophic titers, if one can run them. On the other hand, a low estrogen-progesterone effect without the evidence of pituitary disturbance will indicate either refractory ovaries or refractory endometrium. Here the differentiation can be made accurately by estrogen and pregnandiol studies, theoretically.

In those few cases with physical abnormalities and endocrine abnormalities, both conditions were corrected, but the case was listed under the endocrine condition as it was thought to be the more serious of the two conditions.

Treatment

Treatment resolves itself into three periods: (1) preconceptional, (2) postconceptional, and (3) period of threatened abortion.

The treatment in this series was directed primarily at the factor to which the previous abortion was attributed. They were all given the usual general instructions. Since observation with their previous abortion had indicated that transportation to the hospital aggravated the condition, all were instructed to go to bed immediately should they develop the least vaginal bleeding or uterine cramps. The attending physician was to be notified at once. The patients were not removed to the hospital until (or unless) they passed tissue which was shown to the physician. No complications arose to cause regret of this procedure, as only one hemorrhaged sufficiently for alarm, and none became infected.

The preconceptional and postconceptional treatments for the responsible factors were as follows:

Infantile Uterus.—These patients were given 0.5 mg. of diethylstilbestrol in the first half of the cycle, followed by 10 mg. of progesterone daily (orally) and

No patient bleeding during the first five months was found to have anti-Rh antibodies, but tests were run only during the last few years of the study. The paternal influence could not be evaluated in this series, but it would seem that only in the very unusual case would it play a part, and, therefore, may be considered negligible. This study has led the author to feel that the causes may be listed as: (1) maternal or environmental, and, (2) ova with defective germ plasm. The latter cannot be disproved from this study, but the indications are that it plays no part except perhaps in the very rare case.

Vitamin Effect.—Moore and co-workers, by feeding a diet deficient in vitamin K, observed abortion in all animals.

Javert and Stander found deficiency in vitamin C in 69 per cent and deficiency in vitamin K in 72 per cent of pregnancies studied. Both were low in 61 per cent.

In the writer's experience, abortion will occur with prothrombin levels of 50 to 60 per cent of normal, and bleeding frequently occurs with levels as high as 85 per cent of normal. In his experience vitamin E has been of no demonstrable value at all. No cases with low vitamin C alone aborted in this group which were studied for vitamin C levels.

Progesterone Effect.—Progesterone, in the author's experience, has not relieved cramps in women threatening to abort; in fact, many were made worse. It was felt that injecting progesterone would depress the luteinizing hormone from the pituitary and could actually do harm in the long run. Results have been much improved since omitting progesterone, except where definitely indicated by preconceptional study.

Estrogen Effect.—Interdecidual bleeding during the first six weeks, and perhaps later, is many times due to spasm of the spiral arterioles and subsequent relaxation. From the action of estrogen on the vessels it is obvious that it would be more efficacious. These cases will probably stop bleeding anyway.

From endometrial studies following estrogen therapy in nonpregnant women, this author feels that estrogen depresses FSH while at the same time stimulating production of LH. If this is true, the estrogen therapy seems more rational, especially if any treatment is to be used empirically.

Gonadotrophic Hormone Effect.—There is evidence to show that there is an increased concentration of pituitary gonadotrophic hormone in the urine of pregnant patients from the sixth to the twelfth or thirteenth weeks of pregnancy.

I found a direct relationship between the low glycogen content of endometrium and vaginal mucosa and low gonadotrophic hormone secretions. Many of these cases who did not abort under observation had negative pregnancy tests until as late as three months of gestation. The gonadotrophic hormone is found to be highest during the vomiting stage. In those patients who do not vomit, there is a mild to a marked reduction in the serum gonadotrophic hormone.

Deficiency of chorionic gonadotropin is not a frequent cause of corpus luteum failure, since it was below the normal range in only one of 19 cases tested by Vaux and Rakoff in their series. This is an incidence of 5.25 per cent as compared with an incidence of 6.3 per cent in the author's series (see Table I, "Low pituitary function").

Estrogen-Progesterone Effect.—Vaux and Rakoff found a high percentage of habitual aborters who exhibited low pregnandiol titers, and diminished blood and urine estrogen levels occurring any time during pregnancy.

Diagnosis

Usually the physician is handicapped severely when a patient is seen for the first time during a threatened abortion. With absolute rest and quiet a prime indication, he is extremely limited in his examinations, and usually treats empirically without due regard for the cause of the abortion. Therefore,

Low Gonadotrophic (Pituitary) Effect.—This group comprises the most amenable group of habitual aborters. They were treated for a period of three months preconceptionally. In this period, treatment consisted of giving 300 units of chorionic gonadotrophic hormone twice weekly during the secretory phase of the cycle as well as 0.5 mg. of diethylstilbestrol daily during the proliferative phase, increased to 1 mg. plus 10 mg. of progesterone daily during the secretory phase up to within five days and three days, respectively, of the expected menses. When pregnancy occurred the diethylstilbestrol was increased to 5 mg. twice daily and progesterone to 10 mg. three times daily with parenteral injections of each in case of spotting. The chorionic gonadotrophic hormone was increased to 500 units twice weekly. This was in an effort to stimulate better luteinization of the corpus luteum, plus plain substitutional therapy. The substitution part of this routine undoubtedly depresses the remaining pituitary function somewhat, but the gonadotrophic factor seems to compensate for the depression since the results are quite encouraging. This treatment should be kept up until approximately five months of gestation, when it is felt that the placenta will carry the load until about seven months when the treatment should be started again and continued for six weeks or until labor intervenes. A large number of these cases have premature labors, but if treatment is started again at seven months usually they are carried to good viability. Throughout the preconceptional period and during the pregnancy these patients are kept on a 20 per cent protein diet, with special emphasis on a protein meal just before retiring at night. The diet is thought to be most important. One has to be a bit more liberal with the weight gain in these patients as a rule, but toxemia has not been seen to occur in any of them, and fluid balance usually is maintained easily with the diet.

For some reason, perhaps due to pituitary enlargement during pregnancy, subsequent pregnancies in these patients seem easier, usually each one going a little nearer to term. It is not felt that treatment begun in the threatened abortion period will be of much value. If antibodies were formed to the gonadotrophic hormone it was not evidenced clinically, but tests for them were not carried out.

Low Progesterone Effect.—The results in this group have left much to be desired, and it is felt that further studies may lead to better results. In the preconceptional period of three months the patients were given 300 units of chorionic gonadotrophic hormone twice weekly with 10 mg. of progesterone daily during the secretory phase of the cycle. Ephynal acetate (formerly wheat germ oil was used) was given daily in 25 mg. doses to gain whatever effect its similarity of action to progesterone might offer. These patients do not seem to conceive quite as readily as those in the previous group. After conception, the chorionic gonadotrophic hormone was increased to 500 units twice weekly, and the progesterone to 10 mg. three times a day orally. The ephynal acetate was increased to 50 mg. daily. This was continued without interruption up to the period of viability and then stopped. These patients seem to abort at any time during the pregnancy in spite of the placental effect. It is felt that perhaps diethylstilbestrol might have helped in these cases, for its tendency to stimulate the LH factor of the pituitary, and might counterbalance the depressing effect which the progesterone must have on this factor. The treatment during the threatened abortion stage will not be of value if previous treatment has not been given, as most all of these showed negative pregnancy tests on admission to the hospital. Also, missed abortion seems more common in this group.

Low Estrogen-Progesterone Effect.—This group proved to be but slightly more amenable to treatment than the preceding one. These patients were treated from three to six months preconceptionally, and until there was some response

1 mg. of diethylstilbestrol following estimated ovulation to within three and five days, respectively, of the expected menses. This was given for three consecutive months, then omitted for three months. At the end of the first three months' period a dilatation and curettement was done for endometrial studies, and to further stimulate the uterus. Another curettement was done at the end of the second three months when medication was again begun and the patient allowed to become pregnant. When the first period was missed, the hormones were discontinued so as not to interfere with the normal gonadotrophic secretions of the pituitary.

Postconceptional and threatened abortion period treatment, other than general precautions, is felt to be useless. Many of these patients spotted slightly for short periods.

Retrodisplacement of the Uterus.—These patients were advised to wait for three months. At the end of this period the uterus was replaced and a pessary inserted if the uterus were movable. If it were immovable, it was replaced surgically under anesthesia, all adhesions severed, and the pelvis well peritonealized. The pessary was left in place for the first three months of pregnancy. It was felt that the Findley type pessary was superior to others, as it caused less manipulation and trauma to the patient when removed for cleaning. Putting in a pessary and replacing a uterus once the patient is pregnant as well as the knee-chest position and "monkey walk" have all proved hazardous procedures in the author's hands.

Treatment during the threatened abortion period consisted of general measures plus having the patient remain on the abdomen in bed, or, where possible, slowly filling a mercury bag in the vagina. Usually it was found that the pessary had failed to hold the uterus in complete reposition after the weight of the pregnancy was added.

Low Prothrombin Level.—These patients were advised to wait three months. During the week preceding each menses they were treated. In the early cases, before synthetic preparations were available, cabbage juice was given in large amounts. Later, 2 mg. of a good synthetic vitamin K preparation were given intravenously daily for six days. This was continued at monthly intervals after conception so as to precede the menstrual time. If spotting occurred, the medication was immediately begun in 4 mg. doses daily, intravenously, until the prothrombin level was maintained at 100 to 110 per cent of normal. The bleeding was slow to stop once begun, but these patients were found not to abort readily in spite of the bleeding, if the prothrombin levels were kept up. In this group a great deal can be done during the threatened abortion period if the true condition is recognized.

Low Estrogen Effect.—These were advised to wait three months. During this period they were given 0.5 mg. of diethylstilbestrol during the proliferative phase, and 1 mg. during the secretory phase up to five days of the expected menses. When they began trying to become pregnant the drug was continued in 1 mg. doses without interruption. If pregnancy did not occur the menses usually came on time. If the menstrual period were a week late, the medication was increased to 5 mg. daily and increased by 5 mg. every two weeks until about the beginning of the seventh month, and then reduced by 5 mg. every ten days until completely withdrawn or delivery occurred. If not withdrawn by three weeks before the expected date of confinement, these patients usually went past term. If any symptoms of low estrogen or bleeding occurred, the dose was increased by 5 mg. daily until symptoms were relieved. These cases appear to be relatively easily controlled, and only a low per cent even spotted. It is felt that large doses of estrogen given immediately bleeding occurs may be beneficial in the period when abortion is threatening in cases of this type who have not been treated previously.

Conclusion

This study has shown that for best results in the treatment of abortion, and especially the habitual aborters, a thorough preconceptional workup is necessary. The habitual aborter is such from the first abortion, depending on the hormone imbalance, and not simply because nothing has been done until she has aborted three or more times. Especial attention should be given to the endocrine balance as well as to physical defects and vitamin deficiencies. For best results, treatment must be begun preconceptionally, and continued post-conceptionally, as well as when abortion threatens.

Further study along these lines should improve the results with those of the low progesterone and low progesterone-estrogen groups especially.

A check on all patients with a recognized pregnancy test showed that without the above studies and treatment not more than approximately 50 per cent of the abortions can be salvaged no matter what is done. This does not include bleeding from nidation and certain cases of spasm of the spiral arterioles which will likely carry through regardless of the treatment, or whether treated at all.

From this study one may conclude that habitual aborters fall into three distinct groups according to endocrine deficiencies.

No one medication or combination of medications will prevent all abortions, and until this is recognized and steps taken to individualize each case best results will not be attained.

It should be remembered that when chorionic gonadotropins are used preconceptionally, the pregnancy test becomes unreliable when pregnancy is suspected.

An interesting observation was the fact that patients treated with diethylstilbestrol for low estrogen effect alone usually went beyond term if the medication were not stopped at least three weeks before the expected date of confinement; and, also, those patients with low progesterone effect alone comprised the group in which missed abortion occurred. This would seem to indicate that the estrogens play the more important part in the onset of labor.

It has been shown also by these studies that diethylstilbestrol has a much stronger and more direct effect than the natural estrogens which were used early in this study.

The author wishes to express sincere appreciation for helpful suggestions for various aspects of this study to the following: Captain J. E. Porter (M.C.), U.S.N., Ret.; Dr. C. L. Buxton and Dr. C. P. O'Connell, former Naval Reserve Medical Officers; and Dr. Theodore Neustaedter of the New York Post-Graduate Hospital.

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to treatment as shown by vaginal smears and endometrial biopsies taken during both proliferative and secretory phases. They were given 5 mg. of diethylstilbestrol three times a day and 10 mg. of progesterone three times a day on the twenty-first, twenty-second, and twenty-third days of the cycle for at least three months consecutively. When the patient was advised to become pregnant the medication was changed to diethylstilbestrol 0.5 mg. daily during the proliferative phase, increased to 1 mg. during the secretory phase plus 10 mg. of progesterone daily. Urines were collected at five-day intervals for pregnancy tests. As soon as a positive test was obtained the diethylstilbestrol was increased to 10 mg. daily and progesterone to 10 mg. three times a day. The treatment was continued three to four months as it did not seem necessary to continue longer. A few of these patients had premature deliveries but usually at a viable age for the fetus. It is felt that without preconceptional therapy, treatment during the threatened abortion period would avail little even though many of these were still pregnancy test positive on admission. The treatment would hardly improve the decidual state in time to hold the pregnancy except in very rare instances, perhaps, and then environmental effect on the ovum might cause abnormalities of the fetus.

At first it was rather surprising that the results in this group were somewhat better than in the preceding which was principally a low progesterone effect. However, actually, the level is not always low in this group, but in many the uterus required a higher than average level before it would respond, while in others the ovaries failed to respond properly to the gonadotrophic hormone. The results in this latter subgroup parallel very closely those of the low progesterone effect group, while the results in the former subgroup respond quite well to treatment, and are responsible for the increased results in this group as a whole. Unfortunately, the exact results cannot be expressed in percentages since this group was not broken down into subgroups until a considerable time after the studies were begun.

Summary

This communication is a study of abortions over a ten-year period from June 30, 1936, through June 30, 1946, covering some 7,042 pregnancies with 937 spontaneous abortions for an incidence of 15.35 per cent. Of these cases, 356 were lost before the studies were completed. Twenty-seven per cent of the completed group were "habitual aborters" by accepted standards.

The abortions were grouped as in Table I.

Among the group completely studied, there were only 49.7 per cent pregnancy test positive, but this group included only those who actually aborted.

The success with the habitual aborters was 64.1 per cent as against an untreated expectancy of some 27 per cent. The success with the nonhabitual aborters was 98.6 per cent.

The success and failure by groups have been given in Table I.

Basically, the cause of abortion is, in all probability, environmental, but defective ova cannot be ruled out by this study.

The treatment was divided into: (a) preconceptional, (b) postconceptional, and (c) threatened abortion period, and according to the indications manifested by the cause.

Material and Method of Study

It was felt that in a study of this nature repeated observations of the same group of subjects would be the procedure of choice in order to minimize the variation known to occur between individuals. This variation is particularly wide in the plasma lipids; a value of half the average may occasionally be found in an otherwise normal individual, and appears to have no significance as regards well-being. It is important, therefore, to know how widely the plasma lipids in a single individual vary from time to time. Unless this factor is known, no values found can be considered abnormal unless they are outside the normal limits for a given species.

The subjects of this study were unselected and were taken at random from a group of patients in the middle and upper economic brackets.* No evidence of any chronic, debilitating, or organic disease was present in any of the group studied, and no complications of pregnancy were observed. All patients were given routine dietary and prenatal instructions, but no further attempt was made to evaluate each patient's diet. No patient who received any vitamin supplement was included in the study.

The obvious difficulty of registering women early in pregnancy made the number of cases studied during the first trimester smaller than the others. Of the total group of 26 patients, only 16 were observed during all three trimesters; three more were added during the second trimester, and seven during the third. Sixteen of the group were studied during the puerperium. The determinations of the lipid and vitamin A content of the blood were made once during each trimester, and the postpartum period on blood specimens drawn one to two hours after breakfast. It has been shown that ordinary meals cause no measurable increase in the concentration of vitamin A in the plasma for two to six h. urs. Boyd took samples of blood three to four hours apart during a twenty-four-hour period, and found that the concentration of plasma lipids is not markedly affected by the time of day, the ingestion of ordinary meals, or sleep.⁶

The photolorimetric method of Kimble⁷ was used to determine the values for vitamin A and carotene in the blood plasma. The total lipids were extracted from the plasma with alcohol, alcohol-ether, and chloroform, and weighed according to a procedure previously described.⁸

Results

The changes in the plasma levels of lipid and of vitamin A observed during pregnancy and the puerperium are summarized in Table I. During the first trimester of pregnancy the mean plasma vitamin A level for the 16 patients studied was 106 international units. This value approximates the levels previously found and reported in the larger series of normal nonpregnant women.¹ The mean value for total lipid concentrations was 607 mg. per 100 c.c. This compares favorably with the figures reported by Boyd, who found the plasma of normal young females to contain an average of 689 mg. of total lipid per 100 c.c., and by Herrmann and Neumann, who obtained an average value of 590 mg. per 100 c.c. in normal nonpregnant females.⁹

During the second trimester 19 patients were studied. The plasma vitamin A levels ranged from 70 to 178, and the mean had risen to 123 international units. The total lipids ranged from 604 to 988 mg. per 100 c.c., the average being 760.

Twenty-six patients were studied during the third trimester, the majority in the thirty-sixth week. The plasma levels of both vitamin A and total lipids showed a moderate decline, although both still remained well within normal

*The authors wish to acknowledge the cooperation of the Department of Obstetrics in the study of these patients.

PLASMA VITAMIN A LEVELS IN PREGNANCY

Relationship to the Total Plasma Lipids*

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LABORATORY procedures for the measurement of vitamin levels have been developed in the past few years, and are now fairly well standardized.¹ As a result of studies employing these procedures, nutritional requirements are better understood, and the minimum dietary levels thought to be necessary for good health have gradually been lowered.

It is generally stated that the need for vitamin A is increased during pregnancy, and that few pregnant women receive adequate amounts of this vitamin in their diets.² The information which has been compiled to show the inadequacy of such diets, however, compares poorly with the clinical evidence of vitamin A deficiencies. The purpose of the present study was twofold: (1) to evaluate clinically the frequency of vitamin A deficiencies in a group of apparently normal gravid patients receiving no specific diets or vitamin supplements during pregnancy, and (2) to study the relationship of the total blood lipids to the vitamin A levels of the plasma.

Most of the recent studies on the relationship of the blood lipids and the levels of vitamin A in the plasma have been concerned chiefly with the alteration of the blood lipids which occurs when the intake of vitamin A is varied, and with the influence of large test doses of vitamin A on the blood lipids. The results of these studies are controversial. Josephs,³ using rats, found that the ingestion of large amounts of vitamin A caused little rise in the serum level of vitamin A when the blood lipids were low. Others⁴ have reported that hyperlipemia is a frequent, although not a regular, accompaniment of avitaminosis. The drop in the levels of lipids and vitamin A in the plasma during acute infectious diseases has pointed to the apparent relationship of these two substances, and a number of investigators have suggested that the blood lipids might serve as a vehicle for the transportation and storage of this vitamin.⁵

Most instances of hyperlipemia are secondary to abnormal metabolic and physiologic states, such as diabetes, ether, or chloroform narcosis, renal or liver disease, and blood dyscrasias. A study of the relationship of total plasma lipids to vitamin A concentrations in pregnancy provides an opportunity to observe the changes in the level of vitamin A which occur with hyperlipemia developing in otherwise normal individuals under physiologic conditions.

*This study was aided by a grant from the John and Mary R. Markle Foundation.

partum period and lactation than at any other time. The Food and Nutrition Council advises an intake of 6,000 international units daily during the last half of pregnancy, and 8,000 international units daily during lactation. It has been said that few women receive adequate amounts of vitamin A during pregnancy, and Williams and Fralin report that 96.5 per cent of a *selected* group of pregnant clinic patients failed to obtain 6,000 international units of vitamin A daily.² Other writers have suggested that the low plasma levels of vitamin A found in pregnant women justify the administration of this vitamin during the latter part of pregnancy. The incidence of vitamin A deficiency in pregnancy is not known. Clinical manifestations of this deficiency, however, are uncommon.

In human beings, low plasma levels of vitamin A can and do exist without recognizable evidence of a deficiency. Therefore a low level of vitamin A in the plasma is not diagnostic as an *absolute* deficiency. In a previous study of 25 patients taking an inadequate diet, blood plasma levels of vitamin A as low as 50 international units per 100 c.c. were found. Although these patients presented clinical evidence of a B complex deficiency, as manifested by oral and lingual changes and peripheral neuritis, none were found to have any clinical evidence of a vitamin A deficiency—that is, no eye changes, night blindness, or follicular keratitis.¹

In 12 patients with sprue, who lost large amounts of fat-soluble substances in the stool as a result of steatorrhea, plasma vitamin A levels as low as 12 international units were found, and the mean for the group was 48.¹⁰ Nothing to suggest a vitamin A deficiency was observed clinically in any of these patients.

Milam and Anderson, in a nutrition survey of an entire North Carolina rural county, found that only 40 per cent of the persons studied ingested the recommended amount of 5,000 international units of vitamin A daily.¹¹ In this entire survey, however, less than 1 per cent of the persons had plasma levels lower than 50 international units per 100 c.c.

The mean values of plasma vitamin A for the patients in this study were well within the generally accepted normal range throughout pregnancy. Some of the plasma levels, however, were as low as 70 international units. There was nothing to suggest clinically that the nutritional state of these persons was any less satisfactory than that of those having higher levels, or that the lower value had any influence on pregnancy, delivery, the development of complications, or the postpartum course. Little difference was noted in the vitamin A level between the mothers who were nursing infants and those who were not.

These findings and the postpartum rise in the plasma vitamin A without dietary additions or vitamin supplements suggest that the figures usually given as the lower limits of normal for the plasma level of vitamin A are probably high; that fair and adequate storage occurs with lower levels; that satisfactory adjustment at such levels can and does occur; and that a revision of so-called normal values for plasma vitamin A is indicated. Such a revision would be much more in keeping with the clinical rarity of frank vitamin A deficiency in adults, pregnant or otherwise. While no one would deny the need for an ade-

limits. The vitamin A values ranged from 72 to 142, with a mean of 102. The lipid determinations showed a marked variation, ranging from 288 to 966. Eighty per cent of the values, however, fell between 600 and 950 mg. per 100 c.c. The mean value of 691 is comparable to that found by Herrmann and Neumann in patients near the end of pregnancy—780 mg. per 100 c.c.

The final values were determined on 16 patients during the puerperium, usually between the tenth day and the sixth week after delivery. The plasma vitamin A and total lipid levels were again rising, the latter reaching a mean of 843 mg., the highest level observed during the period of study. The rise in the plasma lipids between the first and second trimester, and that occurring post partum were statistically significant.* The vitamin A level showed a marked degree of constancy throughout pregnancy, the highest level occurring during the second trimester, followed by a moderate decline during the third and a gradual postpartum rise. Statistically, there was no significant difference between any of the means. A study of Table I shows that the mean lipid de-

TABLE I. PLASMA VITAMIN A AND TOTAL LIPID VALUES

| TIME OF STUDY | NUMBER OF PATIENTS | VITAMIN A (I.U.) | PLASMA LIPIDS MG. PER 100 C.C. |
|-----------------------------------|--------------------|--------------------------|-----------------------------------|
| 1 to 3 months | 16 | Range 72-180 Mean 106 | Range 388-990 Mean 607 |
| 4 to 6 months | 19 | Range 70-178 Mean 123 | Range 604-988 Mean 760 |
| 7 to 9 months | 26 | Range 72-142 Mean 102 | Range 288-966 Mean 691 |
| Post partum 10 days to 6 weeks | 16 | Range 66-164 Mean 110 | Range 560-1084 Mean 843 |

terminations parallel those for vitamin A, although the highest values for lipids were found during the puerperium.† In the group studied, no single patient at any time was found to have an unusually low plasma value for vitamin A.

The amount of carotene in the plasma was determined along with the level of vitamin A, and was found to range from normal to high. It apparently bore no relation to the plasma levels of vitamin A or of lipid.

Discussion

Plasma Vitamin A Levels.—It is generally agreed that a high blood level of vitamin A indicates an adequate dietary intake and, as a rule, adequate storage; and that a low level in the plasma is an index of a vitamin A depletion. In persons on their usual diets there is little diurnal variation in the plasma levels of vitamin A, and in normal adults months are required to decrease the level of vitamin A in the plasma by withdrawing it from the food. The level of A in the plasma will be reduced by decreased intake, interference with absorption, or increased metabolism, and occasionally by abnormal excretion or mobilization. The decrease in the plasma level of the vitamin precedes clinical evidence of a deficiency.

It has been accepted that pregnancy increases the need for vitamin A, and that the amount of vitamin A required by the body is higher during the post-

*The authors are indebted to Dr. C. N. Herndon for statistical criticism of the results. The "T" test was used for judging the significance of difference between means.

†The relationship of the values is shown in the scatter graph (Chart 1) where a significant correlation between the vitamin A and total lipid values was found (Correlation coefficient = 0.522 ± 0.129).

When the mean vitamin A level of all those patients having total lipids below 500 mg. per 100 c.c. is compared with the mean vitamin A level of all those patients with total lipids over 900 Gm. per 100 c.c., the difference is statistically significant. The mean vitamin A level for the first group is 82 international units, and for the second 134 international units.

It is possible that the plasma levels of both lipids and vitamin A are dependent on the degree of liver function and mobilization. The low plasma levels of total lipid and vitamin A found during acute infectious diseases could be explained on this basis. Thorbjarsen and Drummond have shown that greater amounts of vitamin A are stored in the liver when the fat content of the liver is increased, and that the administration of choline results in a diminution in the amount of liver fat as well as in the stores of vitamin A.¹²

It would appear that when the plasma lipids begin to rise during pregnancy as a result of increased fetal demands or as a preparation for lactation, a concomitant increase in the plasma levels of vitamin A occurs. Since this increase could not take place in the absence of adequate body stores and intake, the vitamin levels in the plasma represent the nutritional state of the individual. The broad relationship between the concentrations of total lipid and of vitamin A in the plasma during pregnancy and the puerperium is in keeping with the experimental work which suggests that the plasma lipids serve as a vehicle for vitamin A and allow its accumulation in the blood.

Conclusions

In a study of a group of gravid patients in the middle and upper economic brackets who were not maintained on special diets or given vitamin supplements, the mean plasma levels of vitamin A were found to be within normal limits throughout pregnancy and the puerperium. There was no evidence of a vitamin A deficiency in any of the persons studied, nor anything to suggest that the course of pregnancy or labor was altered in the patients having the lowest plasma level of vitamin A.

It would appear that the levels of vitamin A in the plasma are directly related to the nutritional state of the individual, but that the range accepted as normal is too high, and that satisfactory nutrition and storage do occur with lower plasma levels. There appeared to be no need for vitamin A supplements in the patients studied.

Studies of the total plasma lipids showed the development of hyperlipemia during pregnancy, the highest levels occurring during the puerperium. The patients with the most marked hyperlipemia also showed the highest plasma levels of vitamin A. When the patients with the highest and lowest total lipid values were separated into two groups, the difference between the mean vitamin A levels of the two groups was found to be statistically significant. This finding supports the experimental work suggesting that the plasma lipids may serve as a vehicle for vitamin A.

quate dietary intake throughout pregnancy, it would seem from the results of our study that most estimates of the vitamin A requirements of pregnant women are quite high, and that the administration of vitamin A supplements is unnecessary in ordinary instances.

The question of the importance of *optimal* as opposed to *adequate* dietary intake is not easily answered. Certainly, the administration of fat-soluble vitamins in ordinary therapeutic doses will do no harm.

Total Plasma Lipids

The blood lipids are almost always found to be increased in pregnant women, the increase usually beginning during the first trimester of pregnancy and continuing in the first weeks after delivery. The degree of hyperlipemia is unrelated to the nutritional state of the individual; this condition is known to occur after complete fasting, or in persons on restricted diets, where the inadequate supply of carbohydrates and proteins results in an increased demand for fat as fuel.

RELATION OF PLASMA VITAMIN A LEVELS TO TOTAL LIPIDS

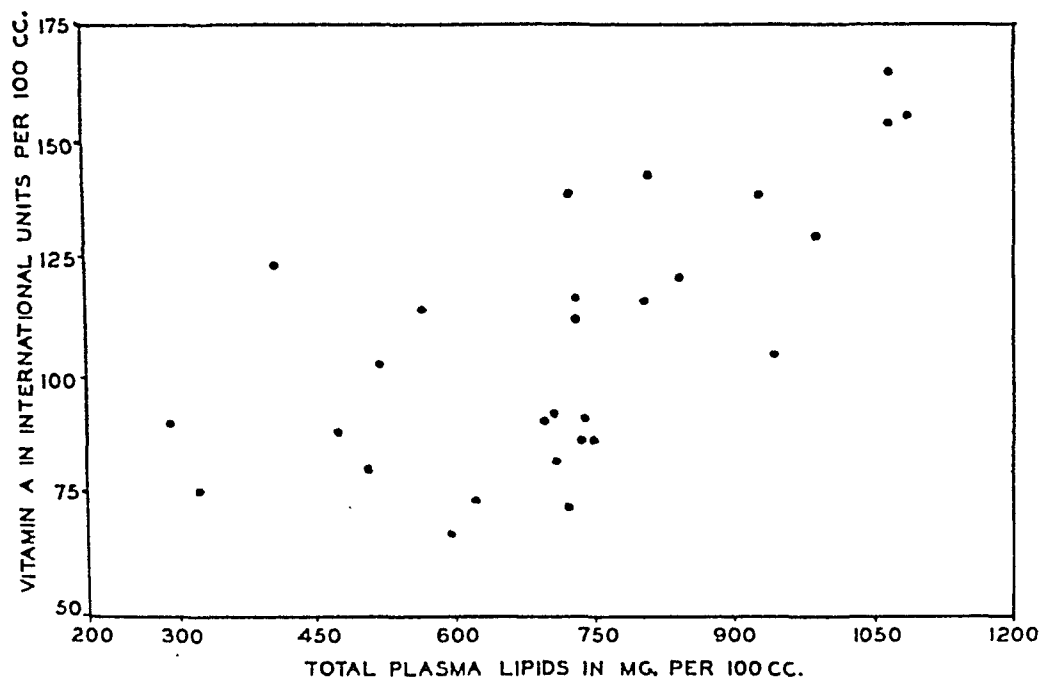


Fig. 1.

In the patients observed in this study a relationship between the plasma levels of vitamin A and the total serum lipids was noted (Table I). In general, patients with high values for total plasma lipids also had high vitamin A levels. The lowest plasma levels of vitamin A were found in those patients having the lowest lipid levels. In no individual patient was a high level of vitamin A found with a definitely lowered total plasma lipid content, or *vice versa*. The correlation is even more striking when it is realized that the concentration of plasma lipids may show considerable variation in normal individuals.

A FURTHER DESCRIPTION OF A SET OF QUADRIOVULAR QUADRUPLETS

(A Study of Dermal Configurations and Tooth Eruption)

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RECENTLY in this JOURNAL a quadruplet pregnancy was described by Dr. B. P. Watson,¹ and through the kind cooperation of the parents of the quadruplets, the writer was permitted to continue the study of the children. A comparison of the dermal patterns of their palms and soles has now been made, which study confirms the findings of Dr. Watson that the children are entirely a fraternal set, having arisen from four fertilized ova. The parents further cooperated during the first year by keeping records of the time of eruption of the children's deciduous teeth, and these data also give evidence of the quadriovular origin of the set.

Cases of quadruplet births in the United States from 1915 to 1942 (in each of which there was at least one live birth) number only 109, giving a proportion of one set of quadruplets in 490,699 confinements.² From 1920 to 1942 the proportion of the sexes in 99 cases was 209 females to 187 males, or 112 females to every 100 males. This ratio is considerably lower than the figure quoted by Watson from the *Statistical Bulletin of the Metropolitan Life Insurance Company*.³ In the latter publication the data used were based on a period of only nine years, from 1933 to 1941, during which time the ratio was 156 females to 100 males. But during these years there happened to be large numbers of females born in each of three years. Over the longer period of twenty-three years, the proportion of females is much lower, being as stated above only 112 females to 100 males. When to the data from the United States there are added 17 more cases from Canada, New Zealand, Australia, South Africa, England, and Wales, the ratio is further reduced to 109 females to 100 males.⁴⁻⁸ However, the trends pointed out by the Metropolitan Life can still be seen, namely, that the sex ratio of females to males increases in the multiple sets from twins to quadruplets. The number of females per 100 males is 94 in single births, 97 in twins, 101 in triplets and 109 in quadruplets. One would expect in quintuplet sets that the females would again be in the majority, and it may be due to the paucity of data that in the 46 recorded cases in which the sex of all infants is given the ratio is only 85.5 females to 100 males.⁹⁻¹⁴

In the 99 sets of quadruplets recorded in the United States census from 1920 to 1942, there were only 71 sets in which all four infants were born alive. Moreover, in the majority of these sets one or more infants died shortly after birth, so that comparatively few sets of quadruplets are later available for study.

A set of quadruplets may have its origin in one, two, three, or four ova, and each type has its special interest from the standpoint of heredity. Members of an uniovular set have a common heredity, since what was intended to be one individual has given rise to four individuals. In the four-egg set there is

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the base of digit III; then the distance between the axial triradius and the distal wrist crease is taken, and the percentage of the latter in relation to the former is calculated. An axial triradius in any position from 0 to 14.9 is symbolized as t , from 15 to 39.9 as t' , 40 and over as t'' . The palmar configurations of the quadruplets are then compared in pairs homolaterally, the average differences being given in Table II. From the latter table it will be seen that the

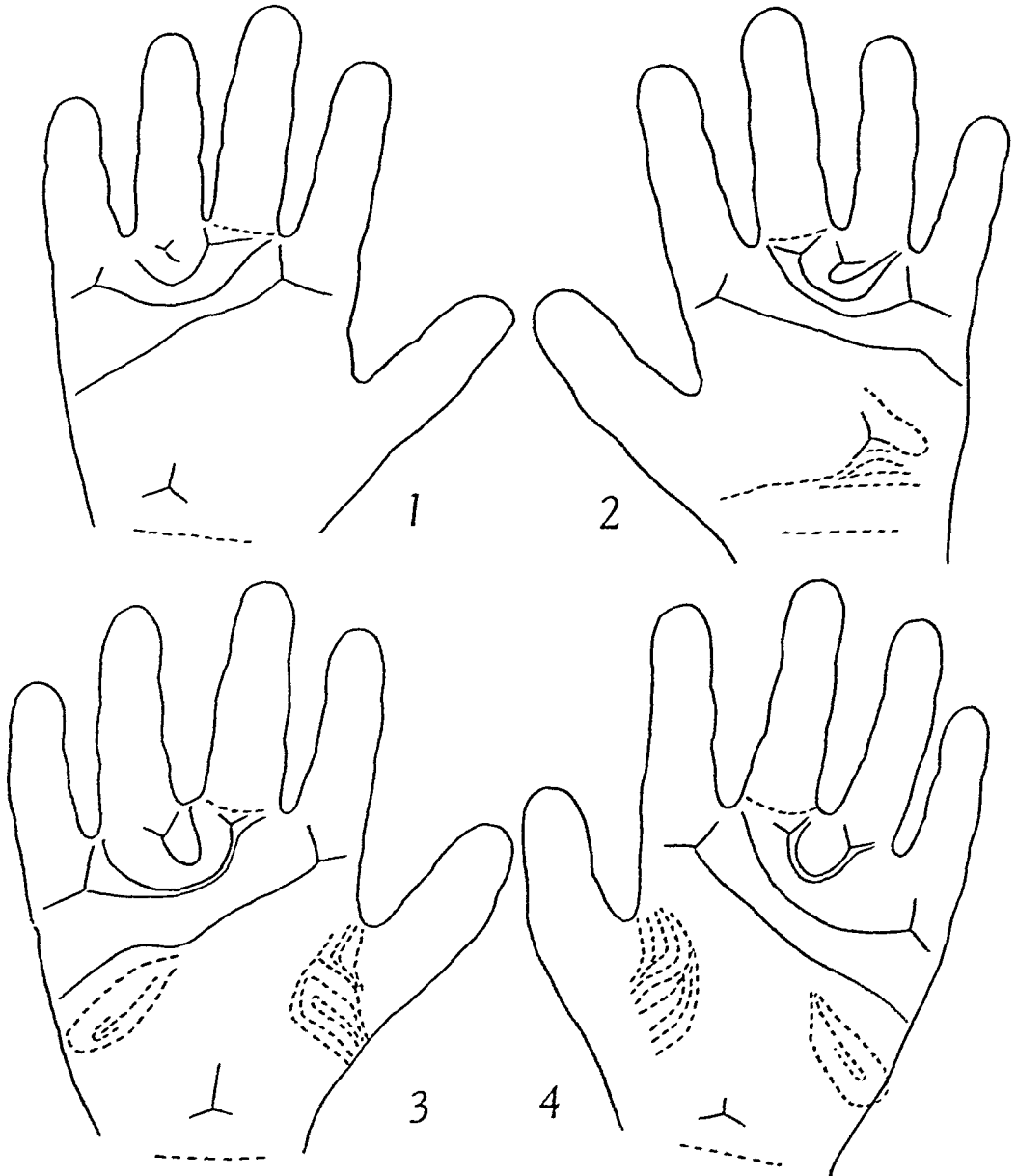


Fig. 1A.—Outlines of the palmar configurations of the Zarief quadruplets. 1 and 2, left and right palms of Isodora; 3 and 4, of Ellen.

averages of these homolateral differences among the Zarief quadruplets are 23.5 per cent for the main lines and 42.9 per cent for the palmar patterns. Differences of this order are indicative of fraternal twinning.

An analysis of the plantar configurations of the Zarief quadruplets also confirms the diagnosis that they are a fraternal set. Outlines of the plantar

no common heredity. The present biological study is concerned with the general problem of establishing the zygosity of such multiple sets from the analysis of dermal patterns. These patterns are particularly valuable because of their complexity and the fact that they are inherited, and also the ease with which they can be recorded and studied.

Until recently many investigators have held the opinion that the structure of the placenta was definitely indicative of the zygosity, but it is now known that uniovular twins may have a dichorionic placenta.^{15, 16} Therefore, the number of choria does not necessarily correspond to the number of ova. The writer has under observation several pairs of identical twins whose dichorionic placentas are stored at the university. In the case of the Zariief quadruplets, here described, it happened that there were four choria corresponding to the four zygotes,¹ but the set might have originated from four, three, two, or one zygotes and still have had four choria.

The Zariief Quadruplets

The Zariief quadruplets were born in New York City on March 29, 1944. They included three girls and a boy. They were palm and sole printed when nine months old. Finger and toe patterns were not taken, since in young infants their small prints are time consuming to make, and in this particular study they had no special value.

The palmar patterns of the quadruplets are illustrated in Fig. 1 and formulated in Table I according to standard methods.¹⁷ The recording of the position of the axial triradii by actual measurement (as suggested by L. S. Penrose) is, however, an innovation. To obtain this position the axis of the palm is measured first from the distal wrist crease to the proximal crease at

TABLE I. PALMAR FORMULAS OF THE ZARIEEF QUADRUPLETS

| | | | | | | | | | | | | | |
|----------|-------|--------|-------|------|----|-------|------------------|-------|--------------------------------|-----|---|------|---|
| Isodora | Left | 11 | X | 7 | 5' | ----- | t(13.5) | ----- | A ^u | 0 | 0 | 0(V) | 0 |
| | Right | 11 | 7 | 7 | 5' | ----- | t'(30.6) | ----- | L ^r /V | 0 | 0 | 0 | 1 |
| Ellen | Left | 11(10) | 9 | 7(6) | 5' | ----- | t(13.6) | ----- | L ^r | L/V | 0 | L | 0 |
| | Right | 11 | 9(10) | 7(8) | 5' | ----- | t(11.2) | ----- | L ^r | V/V | 0 | L | 0 |
| Elaine | Left | 11 | 9 | 7 | 5' | - | t'(16.3)t'(33.7) | - | L ^r /L ^u | 0 | 0 | L | V |
| | Right | 11 | 9(10) | 7(8) | 3 | ----- | t'(19.0) | ----- | A ^u /A ^c | 0 | 0 | L | 0 |
| Benjamin | Left | 9 | 7 | 5' | 3 | ----- | t'(17.4) | ----- | L ^r /A ^c | 0 | M | 0 | 1 |
| | Right | 10 | 9 | 7(6) | 4 | ----- | t'(27.5) | ----- | L ^r /A ^c | 0 | M | L | 0 |

Symbols: A^u, arch ulnar; A^c, arch carpal; L^u, loop ulnar; L^r, loop radial; V, vestige; M, area of multiplication.

TABLE II. HOMOLATERAL DIFFERENCES IN THE MAIN LINES AND PALMAR PATTERNS OF THE ZARIEEF QUADRUPLETS, COMPARED WITH THE MEAN DIFFERENCES FOR TWINS

| SETS COMPARED | MAIN LINES AND AXIAL TRIRADII | | | PALMAR PATTERNS | | |
|---------------------|-------------------------------|------|------|----------------------------|------|------|
| Zariief Quadruplets | Average Difference 23.5 | | | Average Difference 42.9 | | |
| | Mean Diff. | S.D. | S.E. | Mean Diff. | S.D. | S.E. |
| Uniovular Twins | 17.6 | 1.0 | 1.4 | 21.4 | 12.8 | 1.8 |
| Binovular Twins | 31.5 | 9.6 | 2.2 | 32.0 | 15.8 | 8.9 |

Abbreviations: standard deviation, S.D.; standard error, S.E.

TABLE III. PLANTAR FORMULAS OF THE ZARIEF QUADRUPLETS

| | | | | | | | | | | | | | |
|----------|-------|----|---------|----|------|-----|-----|---|---|-------------------------------|----------------|----------------|---|
| Isodora | Left | 15 | 9 | 7 | 15/7 | 13 | 0 | 0 | 0 | 0/L ^d | 0 | L ^d | 0 |
| | Right | 15 | 0 | 9 | 15 | 13 | 0 | 0 | 0 | 0/L ^d | 0 | L ^d | 0 |
| Ellen | Left | 15 | 11 | 9 | 7 | 7 | 0 | 0 | 0 | 0/L ^d | 0 | L ^d | 0 |
| | Right | 14 | 9 | 7 | 7 | 6 | 0 | 0 | 0 | 0/L ^d | 0 | L ^d | 0 |
| Elaine | Left | 15 | 15/11/9 | X | 15 | 15h | 0 | 0 | 0 | W/0 | L ^c | 0 | 0 |
| | Right | 15 | 13/9 | 12 | 10 | 15h | 0 | 0 | 0 | W/0 | L ^d | L ^d | 0 |
| Benjamin | Left | 15 | 9 | 7 | 15 | 13 | Lt. | 0 | 0 | 0/L ^d | 0 ^r | L ^d | 0 |
| | Right | 15 | 10 | 8 | 7 | 13 | 0 | 0 | 0 | 0/L ^d _y | 0 | L ^d | 0 |

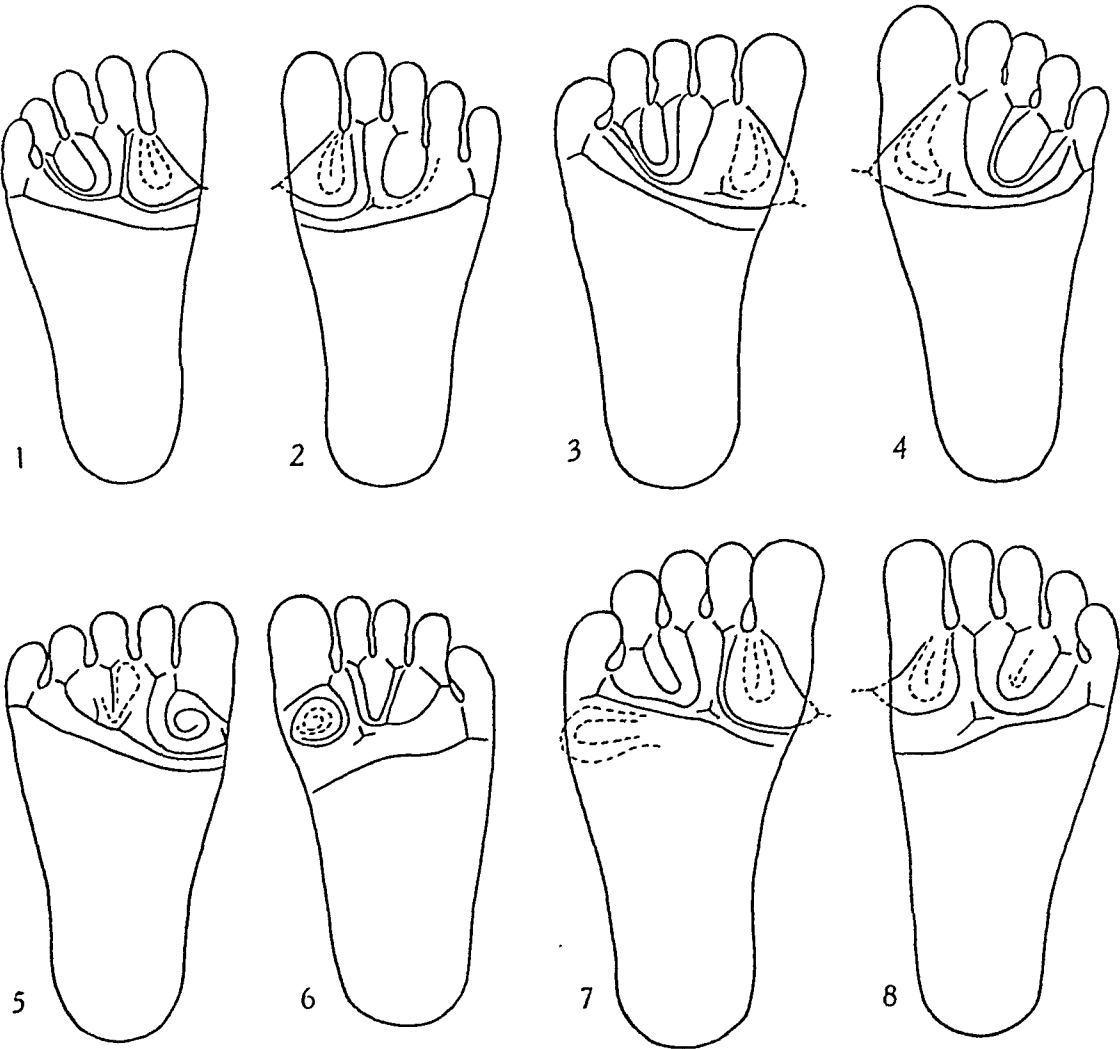


Fig. 2.—Outlines of the plantar configurations of the Zariet quadruplets. 1 and 2, left and right soles of Isodora; 3 and 4, of Ellen; 5 and 6, of Elaine; 7 and 8, of Benjamin.

been assembled by the writer. The differences in the timing of the eruption between the two members of uniovular and binovular sets are summarized and compared with those of the Zariet quadruplets in Table V. The quadruplets are again compared among themselves in pairs. It will be noted from the table that for each individual tooth the mean difference in time of eruption is smaller for sets of uniovular twins than for binovular twins, a result which confirms the assumption that the pattern of eruption of the deciduous teeth is inherited. It will also be noted that the average differences for the Zariet quadruplets are on the whole of an order indicative of a fraternal set.

configurations are seen in Fig. 2 and formulated in Table III. The average homolateral difference amounts to 67.1 per cent for the main lines and 27.5 per cent for the plantar patterns.

Pattern of Eruption of the Deciduous Teeth.—Accurate records of the eruption of the deciduous teeth of the Zarief quadruplets were kept for the first year by the nurse in charge. The times of eruption are given in Table IV.

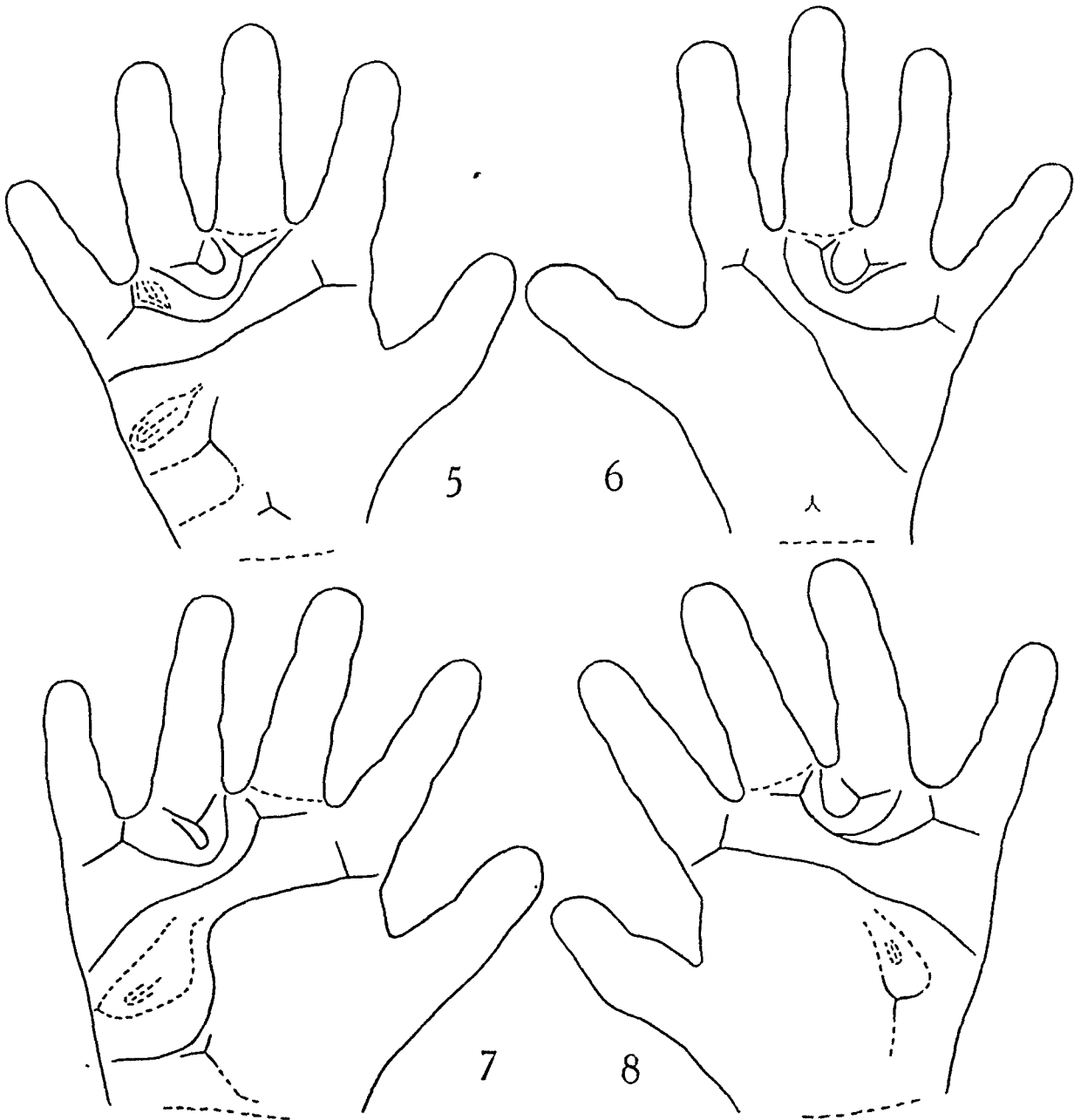


Fig. 1B.—Outline of the palmar configurations of the Zarief quadruplets. 5 and 6, left and right palms of Elaine; 7 and 8, of Benjamin.

It has previously been shown that the pattern of eruption of the permanent teeth is an inherited characteristic,¹⁸ and it seems probable, therefore, that the same should be true for the deciduous dentition. To test this assumption, records of the time of eruption of the deciduous teeth of 64 pairs of twins have

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TABLE IV. AGE IN DAYS AT TIME OF ERUPTION OF DECIDUOUS TEETH OF THE ZARIEF QUADRUPLETS

| TOOTH | AGE IN DAYS OF ZARIEF QUADRUPLETS | | | |
|-----------------|-----------------------------------|-------|----------|---------|
| | ELAINE | ELLEN | BENJAMIN | ISODORA |
| Central Incisor | | | | |
| Upper Rt. | 246 | 291 | 245 | 337 |
| Upper Lt. | 264 | 293 | 263 | 340 |
| Lower Rt. | 208 | 242 | 209 | 263 |
| Lower Lt. | 231 | 247 | 216 | 264 |
| Lateral Incisor | | | | |
| Upper Rt. | 354 | 341 | 270 | |
| Upper Lt. | 356 | 341 | 275 | |
| Lower Rt. | 338 | | | |
| Lower Lt. | 337 | | | |

TABLE V. SUMMARY OF DIFFERENCES IN TIME OF ERUPTION OF TEETH BETWEEN THE TWO MEMBERS OF UNIOVULAR AND BINOVULAR TWINS AND THE ZARIEF QUADRUPLETS (COMPARED AMONG THEMSELVES IN PAIRS)

| TOOTH | UNIOVULAR TWINS | | BINOVULAR TWINS | | ZARIEF QUADRUPLETS | |
|-----------------|----------------------|-------------------------|----------------------|-------------------------|--------------------|----------------------------|
| | NO. OF SETS COMPARED | MEAN DIFFERENCE IN DAYS | NO. OF SETS COMPARED | MEAN DIFFERENCE IN DAYS | PAIRS COMPARED | AVERAGE DIFFERENCE IN DAYS |
| Central Incisor | | | | | | |
| Upper Rt. | (19) | 16.1 | (40) | 25.0 | (6) | 53.5 |
| Upper Lt. | (20) | 20.5 | (39) | 36.1 | (6) | 43.3 |
| Lower Rt. | (20) | 15.0 | (44) | 49.1 | (6) | 33.0 |
| Lower Lt. | (19) | 17.1 | (44) | 51.1 | (6) | 26.7 |
| Lateral Incisor | | | | | | |
| Upper Rt. | (16) | 32.5 | (33) | 55.6 | (3) | 56.0 |
| Upper Lt. | (18) | 28.2 | (33) | 46.5 | (3) | 54.0 |
| Lower Rt. | (15) | 33.0 | (22) | 72.7 | | |
| Lower Lt. | (14) | 15.1 | (23) | 86.7 | | |

Summary

1. A comparative study of the dermal configurations of the palms and soles of the Zarief quadruplets confirms the earlier diagnosis that they are entirely a fraternal set.
2. Comparisons are here made with a new series of mean differences for the dermal configurations of uniovular and binovular twins.
3. Differences in the time of eruption of the teeth of the Zarief quadruplets are compared with new means for uniovular and binovular twins. The differences among the quadruplets confirm the diagnosis of their quadrioovular origin.
4. A survey of 116 cases of quadruplet births gives a sex ratio of 109 females to every 100 males.

The writer wishes to thank Dr. Watson and also Miss H. M. Kelly, R.N., who arranged the necessary contacts for the study.

- I. Ovariogenetic: (tumors developing from tissues of true ovarian structure)
 - A. From the *mesenchymal core* of the ovary.
 1. From fetal cell remnants *without error in sex chromosomes*
 - a. Granulosa cell tumors
 - b. Theca cell tumors
 2. From fetal cell remnants *with error in sex chromosomes*
 - a. Arrhenoblastoma—male
 - b. Disgerminoma—neuter
 3. From interstitial tissues *without sex potential*
 - a. Fibroma
 - b. Angioma
 - c. Myoma and fibromyoma
 - B. From the *surface epithelium* of the ovary (prosoplasia toward the Müllerian duct)
 1. Serous cystoma (tube)
 2. Endometrioma (endometrium)
 3. Pseudomucinous cystoma (cervix)
- II. Nonovariogenetic: (tumors developing from tissues not normally present in the ovary)
 - A. By displacement into the ovary in fetal life
 1. Early—teratoma
 - a. Mature—dermoid
 - b. Immature—embryoma
 2. Late—tissue from structures contiguous to the ovary during embryological development
 - a. Hypernephroma—adrenal
 - b. Mesonephroma—kidney
 - c. Brenner tumor—urogenital epithelium
 - d. Ganglioneuroma—sympathetic ganglia
 - B. By displacement into the ovary in adult life
 1. Metastases of malignant tumors—Krukenberg, etc.
- III. Carcinoma of Undeterminable Histogenesis
 - A. Carcinoma simplex, scirrhus carcinoma, plexiform carcinoma, etc.

Each of the listed benign tumors will have its corresponding malignant form, i.e., serous cystoma, serous cystadenocarcinoma, fibroma, sarcoma, etc. According to Schiller, "There has never been found a small beginning primary carcinoma of the ovary," as has been demonstrated so often in the cervix. On the other hand, it has been demonstrated in many instances that a carcinomatous overgrowth could be traced back to the superficial epithelium of the ovary, and cases have been observed in which tumor portions showing carcinomatous growth have been immediately adjacent to benign tumor growth of the same basic pattern. Therefore, it is felt that probably all malignant forms develop by secondary malignant transformation from a benign tumor.

Discussion of Tumors by Groups

I. Ovariogenetic.—

A. From *mesenchymal core*:

1. From fetal cell remnants *without error in sex chromosomes* (granulosa cell and theca cell tumors):

A CLASSIFICATION OF OVARIAN TUMORS BASED UPON HISTOGENESIS

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THE study of ovarian tumors has received a tremendous impetus of late years due to two main factors. First, the careful study, investigation, and reporting of a goodly number of the more unusual neoplasms, such as the masculinizing tumors and the group included in Novak's feminizing mesenchymomas, owing to their relative rarity and bizarre clinical picture. Fortunately for progress, however, the study of the rarer neoplasms has brought out facts which have shed a few rays of light on their less spectacular cousins. In so doing, the second major change has been wrought; the attempt to work out a truly scientific classification on a histogenetic basis.

Fischel's historic work on the embryology of the ovary, added to careful studies by Meyer, Schiller, MacCarty, Barzilai, and others, has given us a multiplicity of facts and theories which should result in a workable and practical histogenetic classification of ovarian tumors. The anatomicopathologic type of classification has been utilized by most pathologists to date, but from the broader standpoint of a grouping of tumors which may be more accurately divided and studied from the clinical standpoint, it seems to us that the histogenesis should shed additional light, particularly in regard to treatment and prognosis. Certainly, from the radiologic viewpoint, a more universal classification based on a histogenetic background would clear up the present very confused literature regarding the effect of deep therapy. It is still necessary to use descriptive terms to name different neoplasms properly, but it is no longer practical merely to classify these growths into cystic and solid and benign and malignant. In the absence of a universally accepted histogenetic classification, we wish to present a modification of the one suggested by Schiller. We realize that there are certain inadequacies, but hope that it may stimulate controversy and further thought.

We have divided all ovarian neoplasms into three broad classes:

- I. Ovariogenetic: derived from ovarian tissue
- II. Nonovariogenetic: derived from tissues foreign to the ovary,
but found elsewhere
- III. Carcinoma of Undeterminable Histogenesis

Following this basic structure and filling in the subdivisions lead to the following complete classification:

in the normal ovary, produce the granulosa elements of the follicle. If these cells, during mitotic division, should lose an X-chromosome they would become male instead of female in character. They would, therefore, have the potency of the mesenchymal core of the testicle. Thus, they may give rise to a tumor which duplicates the fetal testicle, minus spermatagonia, but containing the male-hormone-producing Leydig cells. Meyer hypothesizes that the tumor originates in male-directed cells persisting in the hilus of the ovary from an early sexually ambivalent stage of gonadogenesis. Both Schiller and Meyer agree that the tumors arise from mesenchyme. Popoff and others have felt that these tumors are actually teratomas with an overgrowth of testicular tissue, and several authors have observed an admixture of teratomatous elements. However, as Meyer has pointed out, gonads are never found in a teratoma. We have classified this tumor as originating from a fetal cell remnant in the mesenchymal core of the ovary, but in contradistinction to the granulosa cell tumor developing with an error in sex chromosomes during mitotic division into an androgen-producing male-gonadlike tumor.

The neuter disgerminoma may also arise as the result of an error in sex chromosomes, an error of differentiation of the cells of the mesenchymal core of the developing ovary. Schiller feels that the mesenchymal cells thus may become sexually indifferent, developing in neither male nor female direction. Since this tumor is frequently found in association with some degree of hermaphroditism, and in both male and female, it would seem probable that there has been some degree of agenesis in the mesenchymal cells, some chromosomal malformation, some lack of stimulus to normal mitosis, and full development of their sexual function. Meyer, who first suggested the name, felt that they originated from "neutral disgerminal cells" found in the mesenchyme of the gonads before the stage of sexual differentiation. Others, such as Ewing and Meigs, felt that this tumor resulted from a one-sided development of a teratoma; Geist felt that they arose from certain cells of the surface epithelium of the anlage of the ovary.

3. From interstitial tissues *without sex potential*:

The fibroma and its malignant form, the sarcoma, make up the majority of tumors in this group. Other odd types such as the angioma, myoma and fibromyoma may be included although some authors deny the existence of the latter two.

Fibroma.—Coe and Geist designate this tumor as arising from the true stroma of the ovary, the musculo-fibrous tissue framework of the organ with its attendant vessels, nerves, and lymphatics. Fischel and Schiller state more specifically that it arises from the mesenchymatous core which normally furnishes the interstitial fibrous stroma. Schiller includes the thecoma as a subgroup of the fibroma, and for many years it has been designated as a xanthro-fibroma. Since, however, the thecoma has definite hormonal activity—which has never been proved in the true fibroma—plus a typical histologic picture it has "come into its own." Hence, for these and other reasons previously noted, we have placed the thecoma with the granulosa cell tumor.

Sarcoma.—As in the case of other malignant ovarian neoplasms it is probable that most, if not all, sarcomas are derived by malignant transformation of a benign precursor. In Barzilai's study of approximately 10,000 ovarian specimens, she was able to find only three sarcomas which she felt were primary; other authors deny their existence. In the majority of instances a benign fibroma probably precedes the sarcoma, and cases have been recorded of this occurring according to Geist. In some instances an origin from the connective tissue of an embryonal teratoma may be possible, and some of the described chondrosarcomas, osteosarcomas, etc., have been felt by some to have this origin.

Histogenesis.—As shown by Fischel, the cells of the mesenchymal core differentiate to form granulosa (epithelial) and thecal (connective tissue) cells. These cells, in the normal process of cell division and growth, eventually mature into the fully formed wall of the normal follicle and normally secrete the female sex hormones estrin and progesterin. Tumors developing from these elements, and secreting estrin and progesterin, may be assumed to have developed by "normal" mitotic division of cells with no change, loss or error in their sex directing chromosomes. Thus, in differentiating the "feminizing mesenchymomas" from the arrhenoblastomas and disgerminomas—which are characterized by reversal or absence of normal female sex hormone production perhaps caused by some change, loss, or error in their sex-directing chromosomes—we have classed them as developing from the "sex-potential" cells of the mesenchyme without error in sex chromosomes.

Thecoma.—Schiller places the theca cell tumor with the fibroma and merely describes it as a luteinized form. However, it seems strange that a simple fibroma, ovarian or otherwise, should become luteinized. Certainly the usual nonspecific connective tissue of the ovary does not possess this potential any more than does connective tissue any place else in the body. Hence, it seems to us that these "luteinized fibromas" must arise from the specific theca or protheca cell elements following some stimulus. It is thus a separate entity with a specific sex-hormone producing potential. Since the theca externa is principally fibrous tissue it is natural that varying degrees of fibroma-like development should be present, while from the lutein-potential cells the lutein areas will develop. In some of these tumors the fibroma element will predominate, while in more definite types the lutein, not luteinized, areas will be most evident.

Granulosa Cell Tumor.—According to Meyer, granulosa cell tumors arise from masses of unused and embryonic granulosa cells left behind in the medulla of the ovary. He states that these embryonic rests may be demonstrated in the ovaries of every full-term female fetus and that they have also been found in the ovaries of adults. Schiller feels that granulosa masses may arise, at any time, from mesenchymal cells whose inherent ability to form granulosa elements was not utilized in the embryo. Years later, due to an unspecified stimulus, these cells will exercise their inherent role. It may be that this "unspecified stimulus" is the unopposed action of the pituitary gonadotrops on the ovary. Schiller's statements are further substantiated by Barzilai and others who have noted that immature mesenchymal elements are found interspersed throughout both granulosa and stromal portions of the granulosa cell tumor. In either instance, these granulosa cell masses or embryonic potential granulosa cells represent a form of embryonic rest or cell remnant which may develop into a tumor at any time.

With the very close relationship, histogenetically, anatomically and functionally, between theca and granulosa cell elements it is not surprising that many thecomas contain granulosa elements and vice versa. von Haam¹⁷ feels that the placement of these "mixed" types of tumors in one or the other category depends upon two factors: (1) the preponderance of one cell type over the other, and (2) the cell type which seems to be most actively proliferating. Novak had proposed the all inclusive term "feminizing mesenchymoma" to include granulosa and thecal tumors, both in their pure and mixed forms.

2. From fetal cell remnants *with error in sex chromosomes*:

The two tumors in this group, arrhenoblastoma and disgerminoma, are relatively rare but of extreme interest.

Histogenesis.—The arrhenoblastoma may, as described by Schiller, originate by an error in sex chromosomes during mitotic division of the "hormone-producing potential" cells of the ovarian mesenchyme; those same cells which,

and thus definitely indicate, by their clinical characteristics, the difference in their histogenetic background. It is probable that the great majority of these tumors arise from the surface epithelium; it is, as yet, impossible to differentiate those derived from other sources except in very exceptional instances.

Endometrioma.—In accord with the present trend of thought, we feel that it is necessary to utilize both Sampson's implantation theory and the theory of abnormal differentiation from celomic epithelium in order to explain entirely the occurrence of various forms of endometriosis. Certainly Sampson's theory has had the majority of adherents for many years, but Sampson himself modified his all-inclusive views of late. In order to utilize a comprehensive and logical classification we have held to the prosoplasia theory in explanation of the occurrence of the relatively rare endometrioma, as defined by Schiller.

II. Nonovariogenetic.—

A. *By Displacement Into the Ovary in Fetal Life:*

1. *Early*—Teratoma: *Mature*—dermoid, *Immature*—embryoma.

Histogenesis.—Multipotent cells, blastomeres displaced into the ovary in fetal life are described by Schiller as the origin of this group of tumors. Others have suggested the theory of parthogenetic development from an ovum; Barzilai feels that this latter theory will best explain the rare chorio-epitheliomatous tumor of the ovary. Most authors feel that origin from a somatic blastomere is the most logical theory so far put forth, although no completely satisfactory histogenetic background has as yet been proved. The term teratoma is the logical one and will cover the whole category. There has been, and still is, considerable confusion in the literature regarding terminology and the term teratoma is frequently misused to denote, of itself, malignancy. The adult teratoma exhibits relatively well-developed structures and a low grade of malignancy, as exemplified by the dermoid in which ectodermal elements predominate, although most of them contain cells of all three layers whose tissues are fully differentiated and tend to form organs. Less well-developed (immature) teratomas, whose potential is less definite, remain relatively embryonic in cell form and proliferative ability. These embryomas thus possess a high degree of malignancy.

2. *Late:* Tissues from structures contiguous during embryological development. (Hypernephroma, mesonephroma, Brenner tumor, ganglioneuroma):

Histogenesis.—Schiller's theory of the histogenesis of this group of tumors is accepted by most authorities, in general principle at least. The ovarian pedicle develops comparatively late, and therefore the ovary remains in close connection with other "regional" tissues for a long period of time. Finally, with the formation of two grooves or folds enclosing the ovarian ligament, it separates from the surrounding tissue. This separation occurs at a time in embryonic life when the cells have already become definitely differentiated. If these folds cut too deeply or are spaced wider apart than normal, non-ovarian tissues may be included. Schiller states that the hilum of the ovary often contains islands of adrenal cortical tissue much more frequently in the newborn than in the adult. Persistence of these inclusions and their neoplastic change give origin to the hypernephroma. Experimental work by Groat, Geist, and Gaines, etc., showed, after bilateral adrenalectomy, a proliferation of cells resembling those of the adrenal cortex present in the ovaries of animals that survived. Groat suggests a metaplasia from ovarian mesenchyme, but others feel this represents a growth of adrenal cell rests.

Schiller, who described the mesonephroma in 1939, explains the origin of this tumor from the inclusion of adjacent mesonephromatous tissue in the same manner as described above.

Angioma.—Novak describes this as being one of the “benign solid tumors, along with lymphangioma and neuroma, which may occur but is exceedingly rare.” Geist states that it is usually a small discrete nodule in an otherwise normal ovary. Meyer and others have reported true cavernous angiomas.

Myoma and Fibromyoma.—The existence of these tumors has been questioned by some authors, but others have reported and described neoplasms containing fibrous and muscle tissue. Origin is from the smooth muscle tissue described in the ovarian core or from the smooth muscle of the blood vessels. The fibromyoma is much more frequent, and Geist quotes Basso as reporting forty-five cases in 1904. Aside from their rarity they behave, generally appear, and are treated like a fibroma.

B. *From surface Epithelium:*

In this group is included the serous cystoma, endometrioma, pseudomucinous cystoma and their malignant forms.

Histogenesis.—The surface epithelium of the ovary (previously designated as the germinal epithelium) originates from the primitive celomic (peritoneal) epithelium and, therefore, has the same origin as the epithelium which forms the Müllerian duct. This surface epithelium frequently invaginates into the cortex and may become pinched off to form the so-called Walthard cysts. These cysts are lined by cells which probably possess the same potentialities as Müllerian duct epithelium. Therefore, the surface epithelium (or the remnants of undifferentiated celomic cells found therein) may develop into a neoplasm with Müllerian characteristics by prosoplasia or metaplasia, according to Schiller. MacCarty has found that the lining epithelium of serous cystomas is occasionally continuous with the surface epithelium. He has also noted that in the contralateral grossly normal ovary there are often found indentations of the superficial epithelium in the form of microcysts and miniature papillomatous growths. According to Barzilai, these same indentations and microcysts may show typical tubal epithelial characteristics. She has thus proposed the name endosalpingioma for the serous cystadenoma with its characteristic high columnar, often ciliated epithelium.

Schiller goes even further and states that since the Müllerian potential of the surface epithelium is so marked, it is reasonable to assume that not only may the cells form neoplasms resembling the epithelium of the Müllerian-derived tube, but also neoplasms resembling the epithelium of the Müllerian-derived uterine cavity and the Müllerian-derived cervix. Thus the endometrioma, duplicating the histologic picture of the endometrium (but not to be confused with the endometriosis of Sampson), and the pseudomucinous cystoma whose tall, pale, mucinous secreting epithelium so closely resembles that of the cervix.

As both Schiller and Barzilai point out, it is not possible to place all pseudomucinous cystomas in the same histogenetic group. Probably there is some relationship, in certain cases, with Brenner cell nests. Barzilai states that some pseudomucinous cystomas originate from Brenner cell nests, and Dockerty states that about 30 per cent of Brenner cell tumors occur in the walls of mucinous cysts. Danforth states that in his study of fifty benign pseudomucinous cystomas no Brenner tumors were found, but that there is present in these neoplasms a basic nuclear type characterized by the presence of a median groove or fold. This nuclear detail is also present in the Walthard rests and Brenner tumors, and may be considered a point in the histogenesis of pseudomucinous cystadenomas. Other pseudomucinous cystomas have been observed deriving from the bowel epithelium of an adult teratoma. Schiller feels that those mucinous cystomas derived from other than surface epithelium may, with increasing knowledge, be eventually shown to be clinically different

utter ignorance of the histogenesis of these forms. Their known extreme degree of malignancy is, we feel, an attribute of their advanced stage rather than of a particular type of neoplasm.

Summary and Conclusion

1. A modification of Schiller's classification of ovarian tumors is presented, along with a discussion of the histogenesis of these neoplasms.

2. It is felt that a clear histogenetic concept is essential for diagnosis, treatment and evaluation of prognosis in the study of ovarian tumors.

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The inclusion of pinched-off elements of the immediately adjacent urinary system may give rise to the characteristic islands of transitional squamous epithelium of the Brenner tumor. Schiller and others, according to Barzilai, have actually observed transition from the rete ovarii to the Brenner epithelium. The relationship between Brenner tumor and the mucinous cystoma has been mentioned previously in this paper. Many authors (Novak, Meyer, Barzilai) feel this indicates that the mucinous portion is derived from the Brenner elements, while others (Dockerty and MacCarty) have thus postulated a teratomatous origin for the Brenner tumors associated with mucinous elements. Danforth postulates a possible origin of the Brenner tumor from Walthard cysts based on his observation of a common intrinsic architecture and nuclear detail. He considers the possibility that a small proportion of pseudomucinous cystomas may arise from Brenner cell rests.

Again, according to Schiller, when elements of the neighboring sympathetic ganglia are pinched off and included in the ovarian pedicle, a ganglioneuroma may develop.

B. By Displacement Into the Ovary in Adult Life:

1. Metastatic or secondary tumors of the ovary:

Histogenesis.—The ovary is a favored site of metastatic involvement arising mainly from two groups of organs; most frequently from the immediately adjacent pelvic organs and less frequently from the more distant gastrointestinal tract. Occasionally primaries are in the very distant organs such as the breast.

The much maligned Krukenberg tumor is the classic example in this group. In general the presence of signet-ring cells is pathognomonic, but other grossly typical metastatic forms may show a very high percentage of glandular formation. In the debatable cases it seems to be a play on words with various authors each forming rules as to exactly what constitutes a Krukenberg tumor. Actually we doubt if Krukenberg (or Marchand, who actually first described these tumors) would himself be as specific or rigid in his own interpretation. It is generally considered that the term indicates bilateral ovarian tumors arising from the mucous membrane of the abdominal cavity. Grossly they are demonstrated by large, solid, lobulated tumors usually preserving the outline of the normal ovary and histologically showing signet-ring cells in a fibromyxomatous stroma. Some investigators have added additional criteria, such as the absence of glandular formation, thus ruling out cases which would otherwise have been included. For this reason the number of true cases varies in different series from 153 to over 300.

The question of the pathogenesis of ovarian involvement has never been satisfactorily explained. Of the present three theories, peritoneal sedimentation, lymphatic spread and blood stream metastases, each has something in its favor and each has its proponents. The peritoneal sedimentation hypothesis probably is the one most generally accepted.

III. Carcinoma of Undeterminable Histogenesis.—

Histogenesis.—As mentioned previously in this paper. Schiller presents evidence that all ovarian malignancies, either sarcoma or carcinoma, are secondary in that they develop by malignant degeneration of a benign neoplasm; that they never arise as a primary malignancy. In the majority of instances there is sufficient evidence histologically to identify the carcinoma or sarcoma with its preceding benign form, as in a serous papillary cystadenocarcinoma. At times, with far-advanced growth, dedifferentiation has gone too far to allow us to trace the malignant form back to its parent benign growth. Therefore, with these tumors, we are forced to use purely descriptive terms such as carcinoma simplex, scirrhus carcinoma, etc. Novak particularly stresses our

bizarre endocrine findings in, for instance, the normal menopausal individual, both from a clinical and laboratory standpoint. These are undoubtedly due to the variations in the regression-egression phase of ovarian-pituitary-adrenal relationship; the titer will depend upon the point in this phase during which the particular study is made.

Ninety per cent of these neoplasms are unilateral and may be partially or completely cystic. Estimates of malignancy vary from 10 per cent¹ to 28 per cent,²² and late recurrences, up to nineteen years,¹⁴ may occur. Conservative surgery is indicated in restricted growths, while radical extirpation plus roentgen therapy is utilized when extension is present.

Report of Cases

We wish to report, and briefly discuss, five patients with granulosa cell tumor. These represent 2.4 per cent of the ovarian neoplasms encountered on the gynecologic service of the University Hospital in the past fifteen years. The age grouping is fairly typical: 14, 40, 60, 66, and 74 years. Three were postmenopausal, and the remaining two were at the two extremes of active sexual life. Complete hormone studies were carried out in only one patient. One patient presented an associated pregnancy at seven months.

CASE 1.—The patient was a 74-year-old woman whose menopause had occurred at 41 years of age 32 years before. There was no further vaginal bleeding until two months prior to entry. At that time she experienced an episode of heavy vaginal bleeding which lasted for one week. Following this she had recurrent vaginal bleeding at two- to three-week intervals. For the ten to fourteen days prior to entry she had had a more or less constant scanty flow.

The past history was essentially negative. Her periods had begun at 13 years of age, were regular at twenty-eight days, and lasted four to six days. She had had five pregnancies and four full-term deliveries. There had been nocturia for ten years with occasional dysuria. Urgency during the few weeks before entry had been marked. There had been no weight loss.

The general physical examination was essentially negative and as expected for a woman of her age. There had been no breast changes. Pelvic examination showed a relaxed outlet; the vaginal mucosa showed clinical evidence of trichomonas vaginalis vaginitis, the mucosa was red and not the velvety smoothness of a typical senile mucous membrane. The cervix was grossly normal, with an old transverse laceration. The uterus was the size of a normal adult functioning organ, freely movable and regular in outline. The adnexa presented, on the right side, an eight centimeter, firm, freely movable, nontender ovarian mass.

The initial laboratory data showed a normal white blood count, slightly decreased red blood count and hemoglobin, and a slightly elevated sedimentation rate. The PSP was 35 per cent in two hours, but the BUN was 13.2, and the urine was negative. The Wassermann reaction was negative, and the electrocardiogram was suggestive of hypertensive heart disease. Pre- and postoperative endocrine data will be noted in the table.

On April 6, 1940, dilatation and curettage revealed a moderate amount of endometrium. At laparotomy, immediately following, the uterus was moderately enlarged, and presented a small median cleft representing a slight congenital malformation. The left ovary was about 1.5 cm. in diameter. The right ovary was solid, about 6 cm. in diameter, and appeared orange-colored beneath the capsule. The tumor was freely movable and the capsule was intact. A right salpingo-oophorectomy was done and the patient's postoperative course was uneventful, except that on the third postoperative day profuse vaginal bleeding

GRANULOSA CELL TUMOR

With a Presentation of Five Cases, One With an Associated Seven Months' Pregnancy

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THE historical, histologic, and clinical aspects of granulosa cell tumor have been discussed in detail by many authors.^{1, 2, 8, 12, 13, 15, 23} This tumor is reported to represent about 4 per cent of ovarian neoplasms,¹⁸ although in general, and in a recent review of our own,³¹ 2.5 per cent seems to represent a more accurate figure.

Histogenetically the granulosa cell tumor arises from mesenchyme; either from granulosa cell rests in the medullary portion of the ovary as held by R. Meyer,¹ or by development from unused, undifferentiated pro-granulosal elements of the mesenchyme as postulated by Schillar.¹⁶

The histologic pattern of granulosa cell tumors has been presented and discussed by many.^{1, 12, 13, 15, 20, 21, 28} The picture is confused only in advanced malignant forms, where, as Schiller¹⁶ points out, the anaplasia may obscure the resemblance to normal granulosa cells. Conversely, other tumors definitely not of granulosa cell type may present certain areas suggestive of such an origin.

Endocrine studies have been, in general, sparse and incomplete.^{2, 4, 7} This has largely been due to the failure to recognize the syndrome preoperatively. Studies made have shown the presence of large amounts of estrin in the urine.^{4, 5, 8, 10} Neuman, quoted by Schulze,² reported increased blood estrin. Geist and Spielman,²⁷ Klaften,¹⁹ Gospe,⁷ Palmer,⁴ and others have demonstrated the presence of increased amounts of estrin in the tumor tissue.

In view of the known pituitary depressant action of large amounts of estrin, one would not expect to be able to demonstrate gonadotropic hormone in the presence of the granulosa cell tumor. This has not been, however, a persistent finding.^{2, 4, 6, 10, 21, 24, 29} However, in some of Zondek's work²⁶ he noted that tremendous doses of estrin could be administered to amenorrheic women without lowering the excretion of Prolan A. It is interesting that the demonstration of gonadotropic hormone, by the A-Z test, has been noted principally in post-operative recurrences.^{9, 10}

Our knowledge of the status of pituitary function in the presence of granulosa cell tumor is apparently confused. There are four possible reasons for this: (1) The amount of circulating estrin is relatively low, as noted in patients whose vaginal bleeding is profuse.⁴ (2) The pituitary has become refractory to the depressing effect of estrin. (3) As we have noted, endocrine assays have been too infrequently and incompletely carried out. (4) We must consider the

*The authors wish to express their appreciation to Dr. E. von Haam, who carried out the endocrine assays and reviewed the pathologic specimens.

Inquiry into the patient's past history revealed the following significant points: menarche at 14 years of age with a regular 28-day flow lasting three to five days. Approximately one year prior to entry her periods had changed from a rather scanty three- to five-day flow to a profuse six- to ten-day flow, although the interval remained twenty-eight days. The pregnancy immediately preceding the present one resulted in a miscarriage at the fourth month and was accompanied by an unusually rapid enlargement of the abdomen. Earlier pregnancies had been term deliveries interspersed with miscarriages.

Laboratory tests showed a few white blood cells and numerous granular casts in the urine. Red blood cells were 4.53 million; hemoglobin, 14.5 Gm.; white blood cells were 23,250, with PMN 89 per cent. The BUN was 24, the sedimentation rate was markedly elevated, and the serology was negative. The temperature was 100° F., with a pulse of 96, while the blood pressure was normal. Physical examination was negative except for the presence of a symmetrical, midline, somewhat tender, firm partially movable abdominal mass extending from the pubis to 3 cm. above the umbilicus. Rectal examination revealed no abnormalities, and the mass did not extend into the cul-de-sac. Vaginal examination was not done because of the recent delivery.

On Feb. 5, 1941, laparotomy revealed about a pint of straw-colored, clear, free fluid in the peritoneal cavity. A large, semicystic tumor of the right ovary extended to the liver and was firmly attached to this organ, the transverse colon and the right iliac fossa. The lower pole of the tumor and the ovarian pedicle were free. The pedicle was clamped, incised, and suture-ligated. Adhesions were freed by blunt dissection and the tumor removed intact. Considerable brisk bleeding from the areas of adherence to the liver, colon, and iliac fossa necessitated the placing of two large gauze packs. The packs were removed fractionally over the next eight days, and the patient was discharged from the hospital on the fifteenth postoperative day. Two months after operation she was given a total of 4,000 Roentgen units to the pelvis.

The pathology report was as follows: "The specimen consists of a mass of tissue 22 by 17 by 11 cm. It is lobulated by cysts and lobules of tissue resembling fibroids. On cut section some cysts are loculated, others are large, single, and filled with a greenish-red viscid fluid. On cut section the tumor has a honeycombed appearance; many areas are the color and consistency of beef, and appear to be degenerating." Microscopically the tumor was a granulosa cell carcinoma.

This patient has been traced, and is alive and well five and one-half years after her operation.

Comment.—Schulze² states that "sterility is theoretically to be expected (in the presence of these tumors) through inhibition of the pituitary, and secondarily of the remaining ovary by the hyperestrinism produced by the tumor." She goes on to state that "association of granulosa cell tumors with pregnancy has been recorded twice in the literature, but as the details of neither case are available, it is difficult to evaluate them. One case is mentioned by Szathmary in which the tumor obstructing labor at full term was removed, but he does not give the reference. Slamova, in 1937, records a case of granulosa cell tumor and simultaneous pregnancy in the *Czecho-Slovakian Gynecologic Journal* which is not available to me. Dockerty¹² states that "the presence of intrauterine pregnancy is very rare with granulosa cell tumor, but can occur with small neoplasms." Henderson,¹¹ reporting 21 granulosa cell tumors, stated that "The smallest tumor and the largest in the series were in this group of (six) neoplasms which failed to produce evidence (from clinical history and endometrial biopsy) of estrogen secretion. The smallest tumor was microscopic in size and was accidentally found in an ovary removed along with a pregnant uterus at the time of therapeutic abortion." There is no mention made as to the duration of

necessitated intrauterine packing. This bleeding persisted until the eighth postoperative day. The patient did not develop any of the typical vasomotor phenomena of the menopause postoperatively.

The pathologic report showed hyperplastic cystic endometrium and a granulosa cell tumor of the ovary. There was no microscopic evidence of malignancy.

This patient is alive and well with no evidence of her disease six years after her operation.

The pre- and postoperative laboratory data are as follows:*

| | VAGINAL SMEAR | PROLAN | ESTRIN |
|---------|-------------------|--|----------------|
| 3/11/40 | Treated menopause | 100 m.u./liter | 150 m.u./liter |
| 4/ 6/40 | (Operation) | (Hyperplastic cystic endometrium) | |
| 4/11/40 | Menopausal | | |
| 4/14/40 | | Negative | Negative |
| 4/15/40 | | Negative | Negative |
| 4/16/40 | | 10 m.u./liter | Negative |
| 4/17/40 | | Negative | Negative |
| 4/18/40 | Menopausal | Negative | Negative |
| 4/19/40 | | 30 m.u./liter | Negative |
| 4/22/40 | Menopausal | (Endometrial biopsy—few glands, some still showing estrin stimulation; no cysts) | |

Comment.—This case is typical in all respects, except that the patient falls into the upper age limit so far reported. Varangot,²¹ in 266 cases, found only 12 over 70 years, and 74 years is the oldest we have been able to find reported in the literature. The presence of prolan preoperatively must indicate that the tumor was not forming sufficient estrin to entirely depress the pituitary. Why did the prolan disappear immediately postoperatively? Its appearance, eventually, would be expected in this postmenopausal patient. Others²⁵ have noted up to 25 m.u./liter of prolan in the urine on the eighth postoperative day.

Typical estrin withdrawal bleeding occurred on the third postoperative day. This has been noted by other observers.^{5, 19, 24} Dworzak²⁰ reported a 52-year-old patient who passed an entire decidual cast on the sixth postoperative day. Probably, in our own case, if estrin bio-assay had been done immediately postoperatively, an almost immediate drop would have been noted, as has been reported by others.⁴

Preoperative diagnosis was made on the symptom complex: postmenopausal bleeding in a patient with a palpable ovarian tumor in whom the vaginal smear showed evidence of estrin stimulation, and in whom there was no evidence of fundal carcinoma, but a hyperplastic endometrium. Additional endocrine studies were done and proved confirmatory, but were not necessary for the diagnosis.

CASE 2.—A 40-year-old Negro woman, para vi, gravida viii, entered the hospital on the obstetric service on Jan. 25, 1941. Four hours after entry she spontaneously delivered a 3 pound, 8 ounce premature infant. Her last menstrual period was June 16, 1940, and her estimated date of confinement was March 23, 1941. She had made three visits to the prenatal clinic, two in December and one in January. For the two months preceding delivery she had had recurrent generalized abdominal pain and several attacks of nausea and vomiting. Immediately after delivery the abdomen remained distended and the patient continued to complain of pain. The possibility of multiple pregnancy was considered, but examination and a flat plate of the abdomen revealed the presence of a large intra-abdominal tumor. This was thought to be a mucinous cystoma of the right ovary, and the patient was transferred to the gynecologic service.

Laboratory tests were noncontributory, except for the following: flat plate of the abdomen showed no evidence of fetal skeleton, the Friedman test was negative. Pyelograms showed a dilated right ureter with some back pressure changes in the right kidney. The sedimentation was slightly increased.

Physical examination was normal except for the following: abdomen distended by a large, smooth, semicystic, nontender, movable mass which extended from the pubis to 4 cm. above the umbilicus. The size, shape, and consistency of this mass resembled that of a seven months' pregnancy. Pelvic examination showed a nulliparous outlet, a small cervix, with a slight brownish mucoid discharge from a grossly normal os. The uterus was not palpable, being pushed posteriorly by the abdominopelvic mass. Examination of the adnexal regions revealed that the same mass occupied the entire area on both sides. The patient's secondary sexual characteristics were entirely normal and well developed.

The preoperative diagnosis was merely ovarian cyst, probably right-sided. Unfortunately, none of the patient's symptoms suggested a granulosa cell tumor, and no endocrine analyses were made. At operation, on Sept. 24, 1945, the left ovary was completely occupied by a freely movable cyst with the tube stretched over the surface of the tumor. The uterus was small and in keeping with the patient's age. The right tube and ovary were grossly normal. The right ureter was markedly dilated in its pelvic portion. A left salpingo-oöphorectomy and appendectomy were done, and the patient was discharged on the thirteenth post-operative day after an uneventful convalescence. Examination one year later found her well and free from evidence of her disease.

The pathologic report was as follows: "The specimen was a large cystic mass measuring 22 by 17 by 12 cm. It weighed over 1,000 Gm. The outer wall was translucent in places, in others it was opaque. Veins were noted running beneath the surface. The cyst was filled with an amber-colored, thin, clear fluid. The cyst wall was thin, measuring no more than one to two millimeters, and in places less. The inner lining was smooth. Near one edge was a protuberance nine to ten centimeters in diameter and projecting into the main cyst. This protuberance was a solid, jelly-like mass well encapsulated and partially cystic." The microscopic examination, after special reticulum and fat stains, showed a tumor of granulosa and theca cells with luteinization. The proliferative elements were granulosa cells. The final diagnosis was a granulosa cell tumor, with an abundance of luteinized stroma.

Comment.—This patient, clinically, presented none of the typical symptoms of a granulosa cell tumor in spite of its size. With the presence of large amount of luteinized stroma, it is possible that the estrogenic effect was counterbalanced by a progestin effect. Novak¹⁵ mentions several reported cases in which, with almost complete luteinization, the endometrium presented evidence of marked progestin effect. It is extremely unfortunate that neither an endometrial biopsy nor endocrine analyses were obtained in our case. The microscopic picture bears out Novak's feeling that most of these tumors are mixed types containing both granulosal and thecal elements.

CASE 5.—A 66-year-old white woman was admitted to the hospital with a chief complaint of swelling of the abdomen of about four months' duration. Six months prior to entry the patient noticed a "bearing down" sensation in the pelvis and stated that her "womb" would drop down when on her feet. About three months before entry she noted "lumps" in both inguinal regions and two weeks before entry her umbilicus became red and then purple and was very tender. She had lost about 23 pounds during the year prior to entry. Her past history was essentially negative. Menopause had occurred at 50 years of age and she had had no bleeding since.

the pregnancy. Powell and Black³ reported a case of coincidental pregnancy and an extra-ovarian granulosa cell tumor. This patient had had numerous abortions, and the tumor was discovered and removed three months after a five months' miscarriage. They make the interesting remark that this patient almost invariably menstruated, more or less regularly, throughout all of her pregnancies.

We have been unable to find, in the American literature, any other case of a third trimester pregnancy associated with a large granulosa cell tumor. It is probable that the tumor was present for at least a year before her delivery, as evidenced by the shift in her periods, and that it possibly caused her previous miscarriages. Why her last pregnancy went a full seven months is not clear. Unfortunately, the type of tumor was not suspected until too late, hence no endocrine studies were carried out. Their determination may have furnished a clue to the persistence of the pregnancy.

CASE 3.—A 60-year-old woman was admitted to the hospital on June 22, 1941, with a chief complaint of postmenopausal bleeding. Her last normal period had been twelve years before and there had been no further bleeding until fourteen days before entry. Painless vaginal bleeding had lasted for seven days, and for the seven days prior to entry there had been no bleeding or spotting. The past history was negative. Menarche occurred at 14 years of age, with a regular 28-day interval, and a four- to five-day flow. She had had two normal full-term deliveries. Her laboratory reports were essentially negative, as was her general physical examination. Pelvic examination revealed a somewhat succulent vaginal mucous membrane with a grossly normal cervix. The uterus was smooth, freely movable, and in normal position, but enlarged to about three times normal size. There was a 6 cm., rather firm, nontender, freely movable tumor of the right ovary. Endometrial biopsy, on June 23, showed hyperplastic cystic endometrium. Urinary estrin, on June 24, was reported as "over 100 m.u./liter."

A preoperative diagnosis of granulosa cell tumor of the right ovary was made and at operation, June 27, a nodular, partially cystic, freely movable, 8 cm. tumor of the ovary was removed. The left ovary was atrophic, and the uterus was about three times normal size. Pathologic examination confirmed the diagnosis of granulosa cell tumor of the ovary.

The patient was discharged from the hospital on the seventeenth hospital day after an uneventful convalescence. She did not develop postoperative estrin withdrawal bleeding, but on the eleventh day began to complain of typical "hot flushes." Follow-up, five years after operation, showed that this patient was alive and asymptomatic.

Comment.—This case is typical in almost all respects. A correct preoperative diagnosis was made on the basis of: postmenopausal bleeding, the presence of an adnexal tumor with an enlarged uterus, hyperplastic endometrium, and markedly increased urinary estrin. Further endocrine studies should have been carried out. Although estrin withdrawal bleeding was not noted, the physiologic response was evidenced by the occurrence of "hot flushes."

CASE 4.—A 14-year-old white girl entered the hospital on Sept. 14, 1945, with the chief complaint of abdominal swelling of three weeks' duration. The possibility of pregnancy was denied. Her present illness was apparently of gradual and asymptomatic onset, as the patient's sister first called her attention to the abdominal enlargement. For the two-week period prior to entry the patient had complained of occasional, fleeting, bilateral flank pain.

The past history was essentially negative. Menarche occurred at 12 years of age, with regular, five-day periods every twenty-eight to thirty days. Her last menstrual period was August 19, the preceding period July 20.

of primary granulosa cell tumor. Increased urinary gonadotropic levels, as determined by the A-Z test, may be of some diagnostic value in recurrence of this tumor.

9. Only by carrying out routine and complete endocrine studies in all cases of ovarian tumor, regardless of symptomatology, will sufficient accurate data be accumulated to be of real diagnostic and prognostic value.

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Physical examination was negative except for the following: the abdomen was flat with a small, tender, purple, one centimeter mass in the umbilicus. There was a small, tender, firm, somewhat movable mass in the lower left quadrant. There were bilateral, discrete, tender, enlarged, inguinal nodes. Pelvic examination showed a small uterus with a firm, somewhat movable, irregular, nontender, 10 cm. left adnexal mass. The laboratory examinations were entirely normal except for evidence of a secondary anemia. No endocrine studies were carried out, as the type of tumor was not suspected.

At operation a left-sided ovarian tumor was found with invasion locally and throughout the lower abdomen. The gross mass was removed, and the patient given postoperative roentgen-ray therapy.

The pathologic report was as follows: "The specimen weighed 550 Gm. On one side there were large, soft, mushy nodules, some of which were thin walled and contained fluid. The other side of the tumor consisted of very friable, grossly malignant tissue." Microscopically the slides showed small round and spindle cell types with a peritheliomatous arrangement, highly anaplastic." Diagnosis was "granulosa cell carcinoma of the ovary."

We have been unable to trace this patient, but her clinical picture practically precludes a long life.

Comment.—This case is not typical of the granulosa cell tumor as a group. The absence of vaginal bleeding, and other signs of "rejuvenation" gave no clues and hence no endocrine studies were made. Apparently the hormonal effect of the tumor was not pronounced. Fauvet¹⁷ mentions a similar picture in one of his cases. Geist³⁰ states that there may be no bleeding in postmenopausal patients with granulosa cell tumor. It is interesting that neither of our two granulosa cell carcinomas presented evidence of really marked hormonal effect. Obviously, the amount of hormone produced by individual tumors may vary markedly. There has not, as yet, been sufficient work done to correlate tumor type with the quantity of estrin production.

Summary and Conclusions

1. Five cases of granulosa cell tumor are reported and discussed.
2. These five cases represent 2.4 per cent of all ovarian neoplasms encountered on the gynecologic service of the University Hospital in the past fifteen years.
3. One of the five cases represents the first third trimester pregnancy associated with a large granulosa cell tumor reported in the American literature. Two questionable cases are noted in the foreign literature.
4. One case, only, was completely examined from an endocrinologic standpoint.
5. Two of the five cases were undoubtedly carcinomas, the remaining three exhibited no evidence of malignancy.
6. Age grouping was typical, although none were prepuberty.
7. In typical cases the preoperative diagnosis is self-evident and hormonal studies are obtained. In the absence of typical signs and symptoms endocrine studies are usually entirely lacking. Complete hormonal studies are still relatively rare in the general literature.
8. It is apparent, from our own work and reports in the literature, that gonadotropic endocrine assays are of no clinical significance in the diagnosis

treatment other than the application of ice bags to the breasts for twelve to twenty-four hours in occasional cases of unusually painful engorgement. The results were considered satisfactory if at the time of discharge suppression was complete except for minimal or slight leakage which ceased spontaneously within two days and required no specific therapy. The results were considered fair if breast leakage at the time of discharge was moderate or was associated with either breast tenderness or firmness, but ceased within the next few days at home without supplementary treatment other than ice bags applied to the breasts. Any transient recurrence of lactation was considered only a fair result, provided, it ceased spontaneously within two to three days. Any case requiring supplementary treatment, either in the hospital or for recurrence after discharge, because of persistent leakage and engorgement, or both, would have been considered a failure, but no such case occurred.

Results

In an attempt to find the optimum method of treatment, seven different courses of therapy were carried out in order to establish the shortest possible course producing optimum results (Table I). Three of these (Courses I, II, and III) were considered inadequate and were discontinued. The shortest dura-

TABLE I. COURSES AND RESULTS

| COURSES | | | | | | | | | | | | | | |
|-----------------|------------------------------------|----------|--------|----------|--------|----------|--------|----------|--------|----------|--------|----------|--------|----------|
| | I | | II | | III | | IV | | V | | VI | | VII | |
| Total dosage | 8 mg. | | 10 mg. | | 9 mg. | | 15 mg. | | 12 mg. | | 12 mg. | | 12 mg. | |
| No. of patients | 12 | | 7 | | 14 | | 10 | | 52 | | 57 | | 31 | |
| RESULTS | | | | | | | | | | | | | | |
| | I | | II | | III | | IV | | V | | VI | | VII | |
| | NUMBER | PER CENT | NUMBER | PER CENT | NUMBER | PER CENT | NUMBER | PER CENT | NUMBER | PER CENT | NUMBER | PER CENT | NUMBER | PER CENT |
| Excellent | 10 | 83.3 | 5 | 71.4 | 9 | 64.3 | 9 | 90.0 | 48 | 92.3 | 56 | 98.2 | 29 | 93.5 |
| Satisfactory | 2 | 16.7 | 0 | | 4 | 28.6 | 1 | 10.0 | 3 | 5.8 | 1 | 1.8 | 2 | 6.5 |
| Fair | 0 | | 2 | 28.6 | 1 | 7.1 | 0 | | 1 | 1.9 | 0 | | 0 | |
| Failed | 0 | | 0 | | 0 | | 0 | | 0 | | 0 | | 0 | |
| Course I: | 1 mg. twice daily for 4 days. | | | | | | | | | | | | | |
| Course II: | 1 mg. twice daily for 5 days. | | | | | | | | | | | | | |
| Course III: | 1 mg. thrice daily for 3 days. | | | | | | | | | | | | | |
| Course IV: | 1 mg. thrice daily for 5 days. | | | | | | | | | | | | | |
| Course V: | 1 mg. thrice daily for 4 days. | | | | | | | | | | | | | |
| Course VI: | 1 mg. four times daily for 3 days. | | | | | | | | | | | | | |
| Course VII: | 2 mg. twice daily for 3 days. | | | | | | | | | | | | | |

tion of therapy has been emphasized, since it allows the patient to be observed for possible recurrence after the discontinuance of treatment. Comparison of the separate courses indicates that a total dosage of 12 mg. must be given in order to obtain optimum results without regard to whether treatment was begun before or after the onset of lactation. Varying the frequency of medication or total duration of treatment within reasonable limits produced only minor variations in the final results. When less than 12 mg. was given, as in Courses I, II, and III, the results indicate inadequate treatment. These courses are therefore not included in the following statistics.

Excellent Results

Lactation.—It is of clinical significance to determine the most effective time to begin treatment. Walsh,¹⁰ Douglas,⁵ and others, using various oral estrogens, have reported greater success when treatment was not begun until after the

MEPRANE: AN EFFECTIVE ESTROGEN FOR INHIBITION AND SUPPRESSION OF LACTATION

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SINCE 1938, when Dodds and his co-workers¹ presented stilbestrol as an effective estrogen for oral use, synthetic oral estrogens have been produced in ever-increasing number and variety. This development is partly explained by the need for a more effective and less toxic preparation. The inhibition and suppression of lactation by estrogens, although the mechanism is not yet clearly understood, is not only an extremely useful form of therapy, but also affords a rapid method of evaluating the effectiveness and acute toxicity of any new estrogen. Thus, an estrogen may be judged by the incidence of toxicity or side-effects, the effectiveness or certainty of inhibition and suppression of lactation, the speed of relief from symptoms afforded, and the duration of treatment required.

With the use of these standards of comparison, a new synthetic oral estrogen, meprane, has been studied in the following 183 cases.

Chemical Composition and Relative Potency

Meprane, 3, 4-bis (m-methyl-p-propionoxyphenyl) hexane, is a synthetically prepared estrogen intended only for oral use. Its relative estrogenic activity was determined by the method outlined in the *Memorandum of the International Standard for the Oestrus-Producing Hormone*,² utilizing the effect on vaginal smears of rats receiving the preparation both orally and parenterally. Compared with other estrogens, meprane when used orally was found to be one-half as active as stilbestrol and twelve times more active than estrone. Toxic effects from meprane were not encountered, even when five times the toxic dose of stilbestrol was given.¹¹

Material and Methods

The following consecutive 183 cases include both ward and private patients of the Massachusetts Memorial Hospitals. Only those who were unable to nurse or in whom suppression of lactation was otherwise indicated were treated.

The aim of the project was twofold. First, the optimum course of treatment for inhibition or suppression of lactation was sought. This was done by varying the daily dosage, the frequency of administration, and the duration of treatment. Complaints were noted, and the condition of the breasts and axillae of each patient was observed daily until discharge. Second, a search for acute toxicity or untoward side-effects was made, special attention being given to gastrointestinal disturbances. Comparative laboratory studies intended to evaluate liver, renal, and hematopoietic functions were also done at the beginning and end of treatment.

Results were graded as excellent, satisfactory, fair, or failed. In those graded excellent, inhibition or suppression was complete without supplementary

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in multiparas. This influence is strongly brought out when the results of all the adequate courses are combined; 100.0 per cent of primiparas produced excellent results, compared to only 89.3 per cent of multiparas.

The inferior results encountered were almost evenly distributed between lactating (3 cases) and nonlactating (5 cases), again indicating no appreciable influence due to this factor alone (Table V).

TABLE V. INFLUENCE OF PARITY AND LACTATION ON EXCELLENT RESULTS

| | NUMBER | PER CENT |
|--------------|--------|----------|
| Primiparas: | | |
| Lactating | 28 | 100.0 |
| Nonlactating | 38 | 100.0 |
| Multiparas: | | |
| Lactating | 35 | 91.4 |
| Nonlactating | 49 | 89.8 |

Age.—Age was also a definitely determining factor, since the older age group uniformly obtained better results from therapy regardless of parity, as shown by Table VI.

TABLE VI. INFLUENCE OF AGE ON EXCELLENT RESULTS

| AGE | PRIMIPARAS | | MULTIPARAS | | TOTALS | |
|-------------|------------|----------|------------|----------|--------|----------|
| | NUMBER | PER CENT | NUMBER | PER CENT | NUMBER | PER CENT |
| 15-29 years | 59 | 100.0 | 37 | 81.1 | 96 | 92.7 |
| 30 and over | 7 | 100.0 | 39 | 97.4 | 46 | 97.8 |

Since multiparas were less satisfactorily dried up than primiparas, it might be expected that the older age group would show less satisfactory results. This, however, was not true, since both multiparas and primiparas showed better results in the older age group, the influence of multiparity being felt almost entirely in the younger multiparas. Beyond the age of 30 years, parity did not influence the results.

Therefore, in this series it is apparent that young multiparas were the most difficult to treat successfully, while the presence or absence of lactation had little or no influence.

Suboptimal Results

The results in 8 (5.3 per cent) of the 150 patients receiving adequate therapy were graded as nonexcellent. All these spontaneously dried up within two to three days after discharge, yielding a clinically satisfactory result. There were no failures of inhibition or suppression of lactation in any of the various courses of adequate treatment, and no patient required supplementary treatment for persistent or intense symptoms. No case of breast-caking occurred. Only one case of this group represented a recurrence of lactation, an incidence of 0.6 per cent for the entire series receiving adequate therapy. Analysis of the non-excellent cases revealed that 62.5 per cent were entirely negative except for some degree of leaking; 12.5 per cent had only some degree of breast firmness, while 25 per cent had both leaking and firmness. No patient complained of breast tenderness (Table VII).

When the statistics are analyzed for influencing factors producing non-excellent results, it is of interest to note that all the patients were multiparas. Also, most of these results were seen in patients under 30 years, three patients (37.5 per cent) being between 15 and 25 years old, 4 (50 per cent) between 25 and 30 years, and 1 (12.5 per cent) over 30 years. The presence or absence of lactation and the postpartum day on which treatment was initiated were not significant factors.

onset of lactation. The results of this series, however, show no consistent variation due to the influence of lactation. As seen in Table II, 94.3 per cent of the

TABLE II. RESULTS IN LACTATING AND NONLACTATING CASES

| | RESULTS | | | | | | | | |
|--------------|-----------|----------|--------------|----------|---------|----------|---------|----------|---------|
| | EXCELLENT | | SATISFACTORY | | FAIR | | FAILED | | TOTALS |
| | NUM-BER | PER CENT | NUM-BER | PER CENT | NUM-BER | PER CENT | NUM-BER | PER CENT | NUM-BER |
| Lactating | 60 | 95.2 | 2 | 3.2 | 1 | 1.6 | 0 | | 63 |
| Nonlactating | 82 | 94.3 | 4 | 4.6 | 1 | 1.1 | 0 | | 87 |

87 cases receiving treatment before the onset of lactation had an excellent result, compared with 95.2 per cent of the 63 cases receiving it after lactation had begun.

This impression was confirmed by analyzing all cases receiving adequate therapy, according to the postpartum day on which treatment was initiated (Table III). Of the 17 cases in which it was begun on the first postpartum day,

TABLE III. INFLUENCE OF TIME TREATMENT WAS INITIATED

| POSTPARTUM DAY | RESULTS | | | | | | | | |
|----------------|-----------|----------|--------------|----------|---------|----------|---------|----------|---------|
| | EXCELLENT | | SATISFACTORY | | FAIR | | FAILED | | TOTALS |
| | NUM-BER | PER CENT | NUM-BER | PER CENT | NUM-BER | PER CENT | NUM-BER | PER CENT | NUM-BER |
| 1 | 14 | 82.4 | 2 | 11.8 | 1 | 5.8 | 0 | | 17 |
| 2 | 56 | 98.2 | 1 | 1.8 | 0 | | 0 | | 57 |
| 3 | 36 | 92.3 | 2 | 5.1 | 1 | 2.6 | 0 | | 39 |
| Subsequent | 36 | 97.3 | 1 | 2.7 | 0 | | 0 | | 37 |

only 82.4 per cent had excellent results. Apparently this was due to inadequate continuation of therapy after the third postpartum day, when the majority of patients showed some evidence of engorgement. However, treatment begun on the second postpartum day, before the onset of lactation, achieved the highest percentage of excellent results (98.2 per cent). The cases in which treatment was begun on the third and subsequent postpartum days, when lactation was almost invariably present, showed 92.3 and 97.3 per cent excellent results, respectively. Therefore, although treatment begun on the second postpartum day was slightly superior, no striking differences were noted between inhibition and suppression of lactation.

Moreover, it was the clinical impression that treatment begun not earlier than the second postpartum day gave uniformly optimum results. There was no appreciable difference in the duration of symptoms in patients beginning treatment before the onset of lactation compared with those beginning treatment after onset, the average duration of symptoms for all cases in both groups being 1.6 days and 1.4 days, respectively.

Parity.—Parity was seen to exert a moderate influence on results (Table IV). Without exception, all courses were more successful in primiparas than

TABLE IV. INFLUENCE OF PARITY ON EXCELLENT RESULTS

| | COURSE | | | | | | | | | |
|------------|---------|----------|---------|----------|---------|----------|---------|----------|---------|----------|
| | IV | | V | | VI | | VII | | TOTALS | |
| | NUM-BER | PER CENT | NUM-BER | PER CENT | NUM-BER | PER CENT | NUM-BER | PER CENT | NUM-BER | PER CENT |
| Primiparas | 4 | 100.0 | 23 | 100.0 | 28 | 100.0 | 11 | 100.0 | 66 | 100.0 |
| Multiparas | 6 | 83.3 | 29 | 86.2 | 29 | 96.6 | 20 | 90.0 | 84 | 89.3 |

per cent. Palmer and co-workers,⁷ using diethylstilbestrol on 219 patients, found only 4 per cent failures when the optimum dosage of 5 mg. was given on the first, second, sixth, and seventh postpartum days.

Murphy,⁸ using octofollin, 5 mg. three times daily for four days, had excellent results throughout a series of 20 cases including both lactating and non-lactating patients. Kurzrok et al.,⁹ using ethinyl estradiol in various dosages, obtained from 65 to 94 per cent excellent results and 35 to 6 per cent poor results or failures.

In the present series when an adequate dosage of 12 mg. of meprane was used over a period of three to five days in 150 patients, the results were excellent in 94.7 per cent, satisfactory in 4.7 per cent, and fair in 0.6 per cent. No failures of inhibition or suppression of lactation occurred. No toxic effects were found either by examination of the patient or by laboratory studies done before and after treatment. Meprane is thus shown to be an effective and potent oral estrogen for inhibition or suppression of lactation, apparently without toxic or side effects.

Conclusions

Meprane, a new synthetic estrogen for oral use, has been given a clinical trial in the suppression and inhibition of lactation under carefully controlled conditions. Various dosages and courses of treatment were empirically used, on the basis of an estimate of potency determined by previous animal experimentation. Possible toxic side effects were carefully sought, by both examination and laboratory studies before and after treatment.

One hundred eighty-three patients were given one of seven different courses of therapy. Three courses were eliminated as inadequate. The results of the remaining four courses, including a total of 150 patients were analyzed. No other form of supplementary treatment except the occasional use of ice bags on the breasts for twelve to twenty-four hours was employed.

The optimum course of treatment, as determined by the speed of symptom relief, the certainty of inhibition or suppression, and the shortest possible duration of treatment, was 1 mg. four times daily for three days. The presence or absence of lactation at the time treatment was initiated exerted no influence on the results. The best results were obtained when this course was begun after the first postpartum day. Primiparas responded better than multiparas, and patients over 30 years of age better than younger ones. Patients remaining symptomatic at the time of hospital discharge quickly became asymptomatic, aided only by the application of bags to the breasts. Such symptoms in all cases were minor and transient. No case in any course presented any evidence of toxic side effects as determined by examination of the patient and confirmed by laboratory studies.

A comparison of meprane is made with other oral estrogens used for the suppression of lactation. From this preliminary study, meprane appears to be definitely superior in the percentage of excellent results, the short time over which treatment need be continued, and the complete lack of toxic side effects.

Summary

Meprane, a new synthetic estrogen for oral use, has been given a clinical trial.

TABLE VII. ANALYSIS OF NONEXCELLENT RESULTS

| CASE NO. | LACTATION | PARITY | AGE (YEARS) | SYMPTOMS |
|----------|-----------|--------|----------------|---|
| 319621 | Yes | M | 35 | Slight firmness |
| *320014 | Yes | M | 18 | Slight leakage |
| 321018 | No | M | 29 | Slight leakage |
| 322302 | No | M | 27 | Moderate leakage |
| 320971 | No | M | 25 | Slight leakage |
| 318378 | Yes | M | 28 | Slight leakage |
| 318924 | No | M | 24 | Slight firmness; slight leakage (unilateral) |
| 319550 | No | M | 23 | Moderate firmness; moderate leakage |

*Recurrence.

Thus, inspection of the suboptimal results confirms the findings in the excellent group; i.e., the less satisfactory results occurred entirely among multiparas, and chiefly in patients under 30 years of age.

Toxic Side Effects

Patients were examined daily to discover possible side effects, particular attention being paid to gastrointestinal disturbances in relation to therapy. Laboratory studies including urine analyses, hemoglobin, nonprotein nitrogen, and total protein determinations were also done at the beginning and end of treatment.

Clinically no evidence of toxicity occurred. This was supported by laboratory data, which remained unchanged except for effects attributable to recent labor and delivery. A rising hemoglobin and total protein with a falling nonprotein nitrogen were consistently noted, particularly in patients having sustained a long labor or an excessive blood loss at the time of delivery. Small amounts of sugar and albumin were usually noted in the urine, but were transient or had existed previous to therapy, no case showing a persistent increase in either. Thus, Meprane in dosages of 12 to 15 mg. given over a period of three to five days appears to be without acute toxic side effects.

Comparative Results

It is of interest to compare our findings with the use of Meprane for inhibition and suppression of lactation with those of other investigators who employed various oral estrogens for the same purpose. Due to the large volume of literature, only a few of the more recent and typical reports will be compared.

Stilbestrol is perhaps the commonest oral estrogen previously used. Fields³ reported 150 cases in which treatment with stilbestrol was begun forty-eight hours after delivery before the onset of lactation; there were 5 per cent failures. Of an additional 150 patients, in whom treatment was begun after a short period of nursing, 14 per cent suffered either breast discomfort, engorgement, or leakage during treatment, and 2.6 per cent had leakage after discontinuance of treatment. Fields also found that in rare cases stilbestrol had no obvious effect on lactation. Barnes⁴ reported 60 per cent successful results with stilbestrol, 41 per cent with dienestrol, and 38 per cent with hexestrol. In 23.5 per cent of all his cases lactation recurred, and in 2.2 per cent some toxic effects were exhibited.

Douglas and co-workers⁵ using diethylstilbestrol, reported 33 per cent successful results when treatment was begun before lactation and 40 per cent when it was begun after the onset of lactation. Diddle and associates,⁶ using diethylstilbestrol, reported 63 per cent good results, 25 per cent fair, and 12 per cent failures. With alpha-estradiol the percentages were 37, 38, and 23

A CLINICAL STUDY OF A NEW SYNTHETIC ESTROGEN

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AN ORALLY effective synthetic estrogen, 3, 4-bis (m-methyl-p-propionyxy-phenyl) hexane* has been used during the past ten months in the Endocrine Clinic, Jersey City Medical Center, for the treatment of 43 menopausal patients in 71 courses, for two cases of premenstrual tension, one primary amenorrhea, one secondary amenorrhea, and one severe migraine. This report exclusively confines itself to the first group—menopausal patients.

Method of Investigation

3, 4-bis (m-methyl-p-propionyxy-phenyl) hexane was administered to 43 patients in 71 courses. Subjectively, the effectiveness of the drug was noted by the relief of symptoms. Objectively, the vaginal smear method of Papanicolaou and Shorr was employed as an index. Endometrial biopsies were taken with Novak curette, and the vaginal Ph was determined by the use of nitrazine paper.

More detailed studies were carried on in several selected cases. Tests given were quantitative blood and urine estrogens, basal metabolic rate, blood cholesterol, nonprotein nitrogen and blood counts. A weekly record was kept of the patients' bodily weights.

Analysis of Results

Of the 43 menopausal patients treated, 18 were Negro and 25 were white. Menopause was spontaneous in 26 patients, and was of the artificial type in 17.

Symptoms

The symptoms were classified according to Sevringhaus,¹ and are recorded in Table I.

The only symptom which was unaffected by this therapy was arthralgia. Two patients complained of vague joint pains and stiffness. It was in these two patients also that the hot flashes were only slightly improved.

Patient F. R., aged 52 years, was first seen on March 21, 1946, for amenorrhea of nineteen months' duration. She began having hot flashes, sweating, melancholy, insomnia, and vague joint pains and stiffness six months prior to visiting our clinic. Vaginal smear was reaction II. She was given this estrogen 1 mg. three times a day for six weeks. Hot flashes, sweating, and Melancholy improved slightly, but the other symptoms remained unchanged, although her vaginal smear was in full reaction IV at the end of the therapy.

Patient R. A., aged 44 years, paid her first visit to our clinic on Feb. 28, 1946, with the chief complaint that of innumerable hot flashes, joint pain, fatigue, and insomnia. Her vaginal smear was reaction III. She was put on this medication of 1 mg. three times a day for six weeks, with all her symptoms but slightly improved.

*3, 4-bis (m-methyl-p-propionyxy-phenyl) hexane is distributed under the name of "Meprane" by Reed and Carnrick, Jersey City 6, N. J.

Seven different schedules of dosage were given to a total of 183 consecutive cases. Three schedules were eliminated as inadequate. In the remaining four schedules, including 150 patients, the results were as follows: excellent, 142 patients (94.7 per cent); satisfactory, 7 patients (4.7 per cent); fair, 1 patient (0.6 per cent); failures, 0.

The optimum schedule of dosage was 1 mg. four times daily for three days. The results of this schedule were as follows: excellent, 56 patients (98.2 per cent); satisfactory, 1 patient (1.8 per cent); failures, 0.

The influence of lactation, parity, and age have been analyzed.

No toxic side-effects were noted.

A favorable comparison of meprane with other oral estrogens used for suppression of lactation is made.

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on 1 mg. maintaining dose after the complete relief of symptoms. Most of these patients are now on this regime, and some of them have been symptom-free for over four months.

The 71 courses were given in the following manner:

Group I—1 mg. three times a day

- 21 first courses for 4 weeks
- 3 first courses for 3 weeks
- 4 second courses for 3 weeks
- 4 second courses for 2 weeks

Group II—1 mg. twice a day

- 15 first courses for 4 weeks
- 4 first courses for 6 weeks
- 20 second courses for 3 weeks

An outstanding feature of this synthetic estrogen was the fact that patients began to feel definite therapeutic effects within two to three days. Over 90 per cent of the patients volunteered the information that the number of hot flashes began to diminish about forty-eight to seventy-two hours after taking the tablets. Patients who took 2 mg. daily did fully as well as patients who took 3 mg. daily, with the exception, perhaps, that the full effect took place a few days later in the group taking 2 mg. per day.

We have obtained satisfactory cures in 64 courses out of 71, or 90.1 per cent, which is a very high index for an oral estrogen. Moderate improvement was obtained in five, and no relief in two. The background of the two patients who were refractory to this estrogen was mentioned above.

Vaginal Ph

When the estrogen titers are high there is an increased glycogen content of the superficial cell layers and vaginal secretions are acid. On the other hand, when low estrogenic titers are present, the glycogen content of the vaginal epithelial cells is minimum, and the Ph of the secretions is toward alkalinity. Estrogenic therapy restores the vaginal Ph to its normal state.

The Ph was studied by the use of nitrazine paper.

| | |
|-------------------------|--------|
| Ph 4.5—yellow | } acid |
| 5.0—yellow brown | |
| 6.0—yellow green | |
| 7.0—green—neutral | |
| 7.5—green blue—alkaline | |

On only 27 occasions vaginal Ph was beyond the range of 7.5. This turned acid gradually during the course of therapy. It was noted, however, that the Ph changes took place a few days ahead of the vaginal cytology.

Vaginal Smears

The vaginal cytology was classified according to Geist and Salmon.²

Reaction I.—Advanced estrogen deficiency. This is characterized by the complete absence of cornified cells and the preponderance of leucocytes and deep cells.

Reaction II.—Moderate degree of estrogen deficiency. The smear shows a variable number of irregularly shaped large epithelial cells, deep cells and leucocytes.

Reaction III.—Slight degree of estrogen deficiency. This smear is characterized by a predominance of irregularly shaped epithelial cells, occasional deep cells and leucocytes.

Reaction IV.—The smear shows mostly cornified epithelial cells. Leucocytes and deep cells are usually absent.

TABLE I. SYMPTOMS

| AUTONOMIC AND PERIPHERAL NERVOUS | NUMBER OF CASES | CURED | IMPROVED | UNAFFECTED |
|-------------------------------------|--------------------|-------|----------|------------|
| Hot flashes | 43 | 41 | 2 | 0 |
| Irritability | 39 | 39 | 0 | 0 |
| Sweating | 40 | 40 | 0 | 0 |
| Chills | 40 | 40 | 0 | 0 |
| Palpitation | 20 | 18 | 2 | 0 |
| Dyspnea | 4 | 4 | 0 | 0 |
| Vertigo | 31 | 31 | 0 | 0 |
| Headaches | 4 | 2 | 2 | 0 |
| Paresthesia | 2 | 2 | 0 | 0 |
| Pruritus | 4 | 2 | 2 | 0 |
| Arthralgia | 2 | 0 | 0 | 2 |
| <i>Psychic</i> | | | | |
| Emotional instability | 7 | 7 | 0 | 0 |
| Melancholy | 9 | 9 | 0 | 0 |
| Weeping | 21 | 20 | 1 | 0 |
| Morbid worrying | 17 | 15 | 2 | 0 |
| Insomnia | 20 | 18 | 2 | 0 |
| Fatigue | 20 | 18 | 2 | 0 |
| Jealousy | 1 | 1 | 0 | 0 |
| Suicidal thoughts | 1 | 1 | 0 | 0 |

The first patient was recently married for the second time. The second patient was cogitating a divorce from her husband who was given to heavy drinking. Such adverse family difficulties have been known to undermine therapeutic effects.

Patients were considered cured when all the symptoms disappeared at the end of the therapy. When one or two symptoms were unaffected they were considered markedly improved. When two or three symptoms were unaffected, as moderately improved. When most of the symptoms were unaffected they were considered as failures. The second courses were given only after an interval of two to three weeks when patients returned with recurrence of symptoms.

TABLE II. DURATION OF THERAPY

| DEGREE OF IMPROVEMENT | NO. OF COURSES | 2 WEEKS | 3 WEEKS | 4 WEEKS | 6 WEEKS |
|--------------------------|-------------------|---------|---------|---------|---------|
| Cured | 52 | 4 | 25 | 22 | 1 |
| Markedly improved | 12 | 0 | 2 | 9 | 1 |
| Moderately improved | 5 | 0 | 0 | 5 | 0 |
| Failure | 2 | 0 | 0 | 0 | 2 |
| Total | 71 | 4 | 27 | 36 | 4 |

Dosages

The dosages were given on the trial and error basis in order to determine the proper therapeutic range. Seven of the patients were first given 1 mg. once a day for over a week, but this dose level was soon discarded because their symptoms were not at all improved. After a few trials we found the optimal dosages to be 1 mg. twice a day or 1 mg. three times a day. Also, from patients' own stories, we have discovered that we were securing the best results by giving the tablets 1 mg. three times a day or 1 mg. twice a day, rather than 3 mg. once or 2 mg. once a day.

Recurrence of symptoms took place very soon after discontinuing the therapy, i.e., seven to ten days. It seemed to be a better plan to put patients

Quantitative blood estrogen was estimated before and after the therapy according to the technique of Frank and Goldberger.⁴ (Table V.)

The urine estrogen was greatly increased after the therapy from twenty to eighty times. The blood levels were likewise elevated in three of four cases tested. This indicated the high estrogenic titers in the body fluids, and showed that a large quantity of the hormone was being excreted through the urine.

Other Laboratory Studies

Basal metabolic rates were followed in ten patients. Only one obese patient had a basal metabolic rate of -19 per cent, and the rest were within the normal limits. There were no variations in basal metabolic rates during the therapy. The patient who had the basal metabolic rate of -19 per cent before the therapy had a rate of -17 per cent at the end of the course, six weeks later. Blood cholesterol, nonprotein nitrogen, and blood counts in the same ten patients revealed no changes during treatment.

The body weights of all the patients were checked at each visit. Most patients gained some weight after the relief of symptoms. The average gain for our 43 patients in 71 courses was 1.55 pounds.

Toxic Reactions

Patients were carefully questioned upon each visit as to any side reactions. Of the 43 patients treated during the 71 courses of therapy, only one patient reacted. Patient G. M. began taking 1 mg. three times a day. At the end of the third week she developed nausea, vomiting, headache, and fever. None of the other patients experienced the slightest discomfort in connection with this treatment.

Summary

1. 3, 4-bis (m-methyl-p-propionoxy-phenyl) hexane is a highly efficient oral estrogen.
2. It relieves menopausal symptoms quickly and thoroughly.
3. Its therapeutic efficiency is 90.1 per cent, and its toxicity is 2.3 per cent.
4. It converted atrophic vaginal smears to the full estrogenic reaction.
5. It altered the vaginal secretions from alkalinity to acidity.
6. Careful quantitative blood and urine estrogen studies showed that it greatly elevated the estrogenic titers of the body fluids.

Conclusion

3, 4-bis (m-methyl-p-propionoxy-phenyl) hexane is a highly efficient oral estrogen with very low toxicity.

My thanks are due to Myra Glickman, B.S., for the technical assistance in this work.

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The vaginal smears of the 43 patients before the therapy were as follows:

| Reaction I | Reaction II | Reaction III | Reaction IV |
|------------|-------------|--------------|-------------|
| 28 | 2 | 8 | 5 |

Only vaginal smears of reactions I and II were followed up carefully.

TABLE III. SMEAR CHANGES DURING THERAPY

| | BEFORE THERAPY | | TIME REQUIRED TO CHANGE FROM R I OR R II TO R IV | | | |
|-------------------------|----------------|-------------|---|---------|---------|---------|
| | REACTION I | REACTION II | 2 WEEKS | 3 WEEKS | 4 WEEKS | 6 WEEKS |
| Group I | | | | | | |
| 1 mg. three times a day | 14 | 1 | 4 | 3 | 8 | 0 |
| Group II | | | | | | |
| 1 mg. twice a day | 14 | 1 | 0 | 4 | 7 | 4 |

It is the writer's belief that vaginal smears taken from the clinic patients are not 100 per cent satisfactory. Vaginal douches, marital relations, and infection can all greatly alter the vaginal cytology. A human assay with a group of hospitalized patients is being carried on. We are hoping that in them, when all the above factors are eliminated and more frequent smears are being taken, we will be able to detect earlier vaginal responses.

Quantitative Urine Estrogens

Quantitative urine estrogens were studied before and after the therapy in six patients (Table IV). Each 24-hour specimen of urine was extracted according to the method of Kurzrok and Ratner.³ The method of assays followed the rules of the standard technique set down by the League of Nations. Each assay was standardized against reference estrone.

TABLE IV. URINE ESTROGENS

| PATIENTS | CONTROL | AFTER THERAPY |
|----------|---------------------|---|
| 1 R. F. | 184.0 I.U./24 hours | 7,730 I.U./24 hours 1 week after the therapy of 1 mg. three times a day. |
| 2 G. C. | 417.0 I.U./24 hours | 12,540 I.U./24 hours 2 weeks after the therapy of 1 mg. three times a day. |
| 3 G. M. | 833.0 I.U./24 hours | 16,980 I.U./24 hours |
| 4 R. R. | 598.0 I.U./24 hours | 12,560 I.U./24 hours 1 week after the therapy of 1 mg. twice a day. |
| 5 E. O. | 213.1 I.U./24 hours | 14,010 I.U./24 hours 2 weeks after the therapy of 1 mg. twice a day. |
| 6 A. P. | 188.8 I.U./24 hours | 15,030 I.U./24 hours 2 weeks after the therapy of 1 mg. twice a day. |

TABLE V.

| PATIENTS | CONTROL | AFTER THERAPY |
|----------|------------------------|---|
| 1 R. F. | Negative | At least 2,000 I.U./Liter 1 week after the therapy of 1 mg. three times a day. |
| 2 E. O. | At least 25 I.U./Liter | At least 750 I.U./Liter 2 weeks after the therapy of 1 mg. twice a day. |
| 3 G. B. | Negative | Negative 1 week after the therapy of 1 mg. twice a day. |
| 4 A. P. | At least 25 I.U./Liter | At least 750 I.U./Liter 2 weeks after the therapy of 1 mg. twice a day. |

pediatricians in the meanwhile running off with all, i.e., father, mother, and child, and in consultation conference and cooperation with each or all three). It is conceivable, too, that we might be in conflict therapeutically over the importance of men—one or many—in the history of any reproductivity that is terminated by a menopause. The absence of men or their presence or the uncertainty of too many or too few contacts, in phantasy or reality, cannot be ignored, so believe most psychiatrists, if a menopausal situation is to be observed accurately. Nor must pubertal impact, one's own or those of others in close proximity, be overlooked, so say the psychoanalysts.

Thus prefaced and with our common objective for womanhood—the preservation of optimal femininity and the protection of a constructive motherliness—substantiated, we can safely review the *psychiatric* aspects of the menopause, and in so doing imply some of the therapeutic procedures indicated and acquire the realization, too, that until further research has been accomplished that the exceptions to all our general assertions will be numerous enough in kind and sufficiently advanced in degree as to still create troublesome cleavages in our asserted unity.

The signs of the menopause which are common and whose presence contribute frequently to anxiety, fear, or guilt are easily enumerated for orientation purposes, i.e., vasomotor fluctuations (“flashes” or flushes, sweating, dizziness, “headaches,” neuralgias, etc.); menstruation divergences (increases or decreases, interval changes, discharge changes, etc.); and psychic manifestations (excitability, depressions, insomnia, worry, etc.). In a day-to-day practice, gynecologists and obstetricians establish as good a rapport—as confidential—as psychiatrists do with disturbed womanhood. And these menopausal signs, their severity, and import are as evident to one as they are to the other. The initial distinction we each make arises, in my opinion, is not in the potential pathologies these signs may include or disguise or must be dealt with promptly at the outset, but in the fact that you have, as gynecologists and obstetricians, many more physical manipulations that you can turn to to bring relief, and therefore resort to more quickly. Whereas we are inclined to defer our evaluation to the determination of a life pattern—as related largely to the known factors which were heralded at puberty—and the sequence of events, imagined or in fact, established over the intervening years. This is laborious history taking that is also therapeutic and fraught with contradictions, identifications, and projections both false and factual, all equally motivating to symptoms and to intent. If a gynecologist or an obstetrician with a secure rapport with a patient endeavors to escape this task of evaluation, and even offers a partial release for the patient by a referral to a psychiatrist, many complications may be set in motion, i.e., the rapport is jeopardized, the patient can now infer, discard, or further decline and be additionally perplexed that the signs, in our professional minds, are truly more “mental” (emotional) than bodily (physical). Much more interpretation for referral than is ordinarily given must be practiced if we are to make the reciprocal gains by which we all would advance. By and large, much significant data go unmentioned in the best recorded histories in gynecologic

PSYCHIATRIC ASPECTS OF THE MENOPAUSE*

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GYNCOLOGISTS, obstetricians, and psychiatrists, in reference to the study of womanhood, may, as diagnosticians, seem worlds apart and be made to appear in deep conspiracy, each against the other. As therapists, however, they can aspire to be as one, united in a common objective to aid women to develop their optimal femininity and to achieve motherliness with a minimum of destructive conflict.

Since it is the gross pathologies—the arrestments, deviations, and distortions—and our own professionally personalized interpretations thereof that tend to throw us apart, this presentation will therefore be limited to some aspects of one feature, i.e., the menopause, which we may all agree to as being physiologically initiated naturally, and thereby, we trust, we may discern in it the analysis of our common objective the better. And, although we will still have to contend with the influence of innumerable variables in three major sectors in the status of a given case, endowment, environment, and experience, nevertheless, for the purpose of clarity and unification, we may exclude that block of barren womanhood that reaches the menopause devoid of a history of conception or is childless. Even so, the frustrations and sublimations of reproductivity for women in our present culture so confuse the menopause state and obscure our conjoined efforts as such, broadly speaking, as to threaten our temporary alignment as therapists in general agreement, and with a common objective.

There is a general agreement that that phase of a woman's life when the capacity for reproduction is ending through the termination of menstrual function is the menopause. Furthermore, the descriptive literature in our respective fields is clear and concurred in, namely, that ovulation ceases through altered glandular activity; reproductive organs atrophy; and aging bodily changes traceable to both endocrinal and hormonal action occur. We all are familiar, too, and subscribe to the findings that studies in maturation, growth, and nutritional status, as determined in tissue metabolism, vitamin load, and excretion levels, serum proteins, ketosteroid and estrogen analyses, blood enzyme levels, and creatine/creatinine roles reveal. But the biochemistry and psychophysiology of fetal conduct, the psychosomatic stimulations and residuals of sexual congress, pregnancy, per se, delivery releases and postpartum supplements and nursing regimes—the appraisal of the significance of all these, to be more exact, and upon whom and when and where and for how long—tend to divide us and create dissension if not downright discord (with the

*Presented, by invitation, at a meeting of the Texas Obstetricians and Gynecologists Society at Galveston, Texas, on Nov. 2, 1946.

In either of these situations the therapy to be considered must be basically protective and redirective—away from dangerous compromises, reckless “flings,” exploiting companionships, disparaging rampages, or false retreats. Wherein paranoid features become conspicuous—toward devoted relatives or lifelong acquaintances—it is noticeable that suspicion and vindictiveness become marked, and most psychoanalytic schools would call our attention to sexual arrestments, deeply buried or well sublimated, either latent, overt, or perverted in whole or in part. The hostilities related hereto that are acted out are as likely to be directed toward the therapist as any other, and, accordingly, many of these patients find themselves being transferred eagerly from one therapist to another with here and there a questionable “quack” tossed in for extra measure all around and in sweet revenge!

Depressions, varying from transitory twinges to monopolizing states of melancholia, are common and may be accompanied by moods of ecstasy or elation or not. In some cases the grief and feeling of abandonment or desertion is all too true and justified—for they are engulfed by decline and set apart from others. Potentially suicidal as many are regarded to be, the essentials of therapy should stress in these cases, hygienic measures that strengthen, and a series of interviews which will desexualize the accumulated feelings of frustration, longing, and guilt. In these cases psychiatrists are prone to lay stress upon one's first experiences at the breast, the bowl, the bath, and the bed. The purposelessness and pallor of these depressive states in the menopause may be most misleading—“still waters run deep”—however mild on the surface and it doesn't suffice merely to activate the sluggish or to cap the filling cistern of conflicts. Together we must be more specific in our prescriptions—not simply to rely upon the arousal of interests in sports, artistry, social, or spiritual values, but actually decide on the additional factors gleaned from the individual's total life pattern which interests to deal with for how long and by and with whom and at what place and when, and then share the recorded results. And to curb the overactive cases by order or by drug may bring superficial quiet and simulated improvement, but in their wake the patient may be left to nurture hypochondriacal ideas, and clearly envision the impending doom, if not truly sense the gnawing of a beginning malignancy or to make it right sporting and really arresting confound one professionally with “a tumor that shows life.” In these cases, although the immediate indications for palliative surgery may be expertly explained, the operation agreed to and flawlessly done, yet the cure, so called, does not occur and postoperative adhesions and stricture symptoms soon follow along and the diagnosis is belatedly now referred to as “a psychiatric or a functional condition” though it could have been both undetected or conventionally hidden lifelong and long before the menopause released the barriers to exposure.

One of the better texts, a definitive work in its own name, which delineates from a psychoanalytic point of view the complications inherent in any sex conduct, fancied or factual or inferred, that would profoundly affect the menopause has been written by Deutsch. It would be presumptive, indeed, to dis-

and obstetric clinics and practices, with the excuse that for the time being they are too time consuming to prepare or are irrelevant to actual treatment to be undertaken. This oversight or repudiation of information as currently handicapping or inconsequential may, at a later date, when the onset of the menopause obscures everything, be obtainable only by skillful detection from further distortion by dream or phantasy or compulsive inversions.

Many women not only seek to have allayed disturbing signs, but also must be assured fortification against the extension of retrogressive processes, i.e., beauty loss in particular. Compensatorially, the struggle to preserve this inherent femininity—beauty and biologic productivity, though cessation of the latter may be a welcome relief—assumes a drive or activity that should be recognized early and its dispensation arranged for. You have observed these manifestations many times over. They are so frantic in quality sometimes that you must yearn for a prompt resource referral, for those who abruptly seek another pregnancy to re-experience motherhood, or others who turn to pursuits or skills of a creative nature long dormant, especially since prepubertal days. In most cases we probably would agree as to the direction of therapy in the renewed drive for pregnancy, but the more sublimated creative drive we tend to argue about or dispose of as too superficial to squander our time over, though the degree of emancipation to be accomplished is deeply vested in the quality of the creative urge itself, i.e., intellectual, artistic, or moralistic. The entire field of family constellations is embroiled in this, namely, (1) the separation from one's children and not to feel shelved, (2) the acquisition of an in-law son or daughter and not to be free of jealousy; and (3) the renewal or extension of motherhood by substitution via grandchildren and not to be secretly scheming. It is vital to therapeutic procedure to help one in the menopause to anticipate a functioning role in family life, that does not usurp the lives of kin, or is not a torment to others, but instead aids one to muster her energies into productive pursuits and away from immobilizing debilitating conflicts There is a type of womanhood that in the menopause undergoes a heightened vitality that the layman dubs "dangerous and overdone." She denies her age and tries to belie it and often decries it in her contemporaries. Here in America, accessibility to an overabundant supply of cosmetic devices and purposefully designed fashions to help this self-delusion may be abetted, but actual therapy has to be more inclusive than this, in a postwar period, where men are returned to civilian life with an altered concept of womanhood generally, and much less passive toward the protection that such an older woman has frequently professed to offer.

In the menopause, as the instability or vacillation becomes dominant almost to the point of capriciousness, suggestibility becomes apparent, and exaggeration is common. It is true that these traits lessen inhibitions, arouse stimulating reveries, discolor sound judgment, and discredit symptoms (minimization or exaggeration). All life for some of these suddenly becomes most subjective or surcharged with personalization as their own atrophies and regressions accentuate their own depersonalization. Others, to bolster up an ebbing self-confidence, hurl themselves into a tightly devised isolation or solitary superiority.

we could be at wide variance and even be in conflict ourselves over the relative merits of any one factor and its subsequent appraisal. However, confidence in one another and a cooperative effort to interrelate and to correlate our differences on each case individually would go far to assure to women in the menopause a degree of increased comfort not now available to but a very few.

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cuss the features of sexual adjustments before an informed group of gynecologists and obstetricians, and to furnish you with any information not already well known to you. There is, however, one feature of the menopause, referred to earlier, and explained at length in the book by Dr. Deutsch to which your attention should be called to especially. It is the feature of depersonalization. As the loss of femininity increases and the reproductive capacity diminishes, there comes to the forefront more noticeably in a woman's life in the menopause elements of masculinity. To whatever degree it was masked throughout life or distorted or sublimated or repressed, the physical changes in the menopause help to make these elements more real and the component emotional elements more apparent. It may or may not concern the patient herself. You too may know what to do about it per se, or seek to minimize it or simply condone it as inevitable or "one of those inescapable things we just have to put up with." If shocked in the extreme by it, many women cannot discuss these manifestations openly or freely, and if she is a new patient to you it is exceedingly hazardous to have it brought out by a therapist. Not infrequently it is of grave concern to others, especially to children, and more specifically to husbands, sons, uncles, brothers, or fathers. Many adult men find it excruciating, so to speak, to confer with a gynecologist or an obstetrician when their womenfolk are in the twilight zone of reproductivity and beginning to adopt a masculinity of their own. Many women, too, are reluctant while in the menopause, except for retaliative purposes perhaps, to defend adequately her request uncompromisingly that the male in her life be consulted regarding her own threats of and to masculinity. Personally, I suspect that were we to share the notes of our consultations we would find the preponderance of confirmation that these males are in our psychiatric files—hard as it was for them too to see a psychiatrist—as patients themselves or regarding how best the woman in their lives can be treated or should be handled, whereas she continues blithely to be content to receive gynecologic care, though emancipated well and good from obstetrics. Surely our best united efforts could first be concentrated on these situations—monopolizing to all of us—and perhaps a segment of marital discord could be alleviated and many in middle-age look forward to a happier and a more harmonious old age together than is now anticipated by them. And a further implication beyond the need for a perfected united service between us in these divided situations is that all—gynecologist, internist, obstetrician, neuropsychiatrist, or surgeon—who treat those in the menopause should also be conversant with involutional states and the field of geriatrics. It is a questionable practice that simply takes a woman through the menopause nobly and then leaves her confronted, head-on, with an old age, uninspired and hopeless!

Treatment for the menopause, as outlined by gynecologists or obstetricians, and that which psychiatrists would propose in simplified form is for the most part similar in type, i.e., hygienic, supportive and protective, regulative, and directive. We vary most in the application of disciplinary measures and the evaluation of conflicts as expressed by the patient. Throughout this presentation it is obvious that in the selection of significant factors in our history taking,

TABLE I.

| YEARS | NUMBER OF CASES | AUTHOR, HOSPITAL | INCIDENCE OF CESAREAN | CESAREAN MORTALITY UNCOR- RECTED | CESAREAN MORTALITY FACTOR |
|-----------|--------------------|-------------------------|--|---|---------------------------------|
| 1935-1945 | 10,818 | Thoms, New Haven | average 5.9% ward 3.2% private 9.6% | .31% | 1.8 |
| 1932-1943 | 68,786 | Waters, Jersey City | 2.67% | 1.0% | 2.7 |
| 1931-1944 | 39,709 | Dieckmann, Chicago | 4.74% | .61% | 2.9 |
| 1932-1939 | 27,125 | N. Y. Lying-in | 2.1% | 1.7% | 3.6 |
| 1939-1946 | 8,107 | Gandy, Stamford | 6.5% | .75% | 4.9 |
| 1934-1943 | 1,887 Cesareans | Irving, Boston | average 4.2% ward 3.2% private 6.7% | 1.3% 1.4% 1.1% | 5.5 |
| 1938-1942 | 4,875 | Nash, Kansas City | 7.1% | 1.1% | 7.8 |
| 1932-1941 | 750 Cesareans | Eastman, Baltimore | 5.5% | 1.8% | 9.9 |
| 1931-1941 | 23,396 | Barney, Cleveland | average 6.1% ward 6.3% private 6.0% | 1.7% 3.3% .5% | 10.4 |
| 1932-1942 | 22,754 | Mohler, Philadelphia | average 5.8% ward 3.6% private 9.58% | 1.96% 3.17% 1.15% | 11.4 |

In order to more easily evaluate the statistics contained in the above table and similar tables, I am introducing a new term which I will call the "cesarean mortality factor." In most tables relative to cesarean section there are two variables, the incidence of the operation and the mortality from the operation. The cesarean mortality factor is a combination of these two factors in their proper relation on a basis of ten thousand deliveries. The factor is the actual number of deaths in the institution which may be expected among the cesarean patients for each ten thousand deliveries. For example, if the cesarean factor is five there are five cesarean deaths for each ten thousand women delivering babies. When the cesarean mortality factor is low there are few deaths chargeable to the operation, regardless of the number of operations performed; when the factor is high, there are many deaths chargeable to the operation, regardless of the percentage of operations performed. I feel this gives a much clearer picture of the lives lost as a result of the operation than do simple percentages of operations performed and the mortality percentage for those operations. One would expect that as the number of operations increased the cesarean mortality factor would increase. In general this is true, but the exceptions are outstanding. The institution with the lowest cesarean mortality factor performs operations on 5.9 per cent of all admissions; the institution with the highest factor performs the operation on a similar percentage of 5.8. It should be our aim to keep the cesarean mortality factor as low as possible, regardless of the percentage of operations performed in achieving this end. In Stamford, though we have performed cesareans on 6.5 per cent of our pa-

CESAREAN SECTION MORTALITY IN THE HOSPITALS OF A SMALL COMMUNITY—A DEFENSE OF THE PROCEDURE*

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THE primary purpose of this study is to investigate the frequency of cesarean section in the city of Stamford and to determine whether or not we are practicing good obstetrics, relative to this operation.

Stamford has a population, including several small peripheral communities, of about seventy thousand. There are two hospitals in Stamford. Since the obstetric department in each hospital is approximately the same size, there being a total of 70 obstetric beds, and since the same physicians practice in both hospitals, the figures represent the combined results from the two institutions. Both hospitals are "Open Staff" hospitals with a total of 35 doctors practicing obstetrics in the institutions. The cesarean sections were performed by eight operators. Three of the eight operators do nothing but gynecology and obstetrics, while the other five do general work.

The study covers a period of nearly six and one-half years, from October, 1939, to July, 1946.

During the period of this study just under 99 per cent of the deliveries in the city occurred in the hospitals. Over 90 per cent of the patients were private cases. The private patients received their prenatal care from their own doctor, while the staff cases received similar care from the clinic or had no prenatal care.

Because of the type of obstetrics in Stamford, practically all private cases and practically all delivered in the two hospitals, we should anticipate better results than in those institutions which serve a high proportion of staff cases or are located in a community where there are many normal home deliveries which never reach the hospital records.

Since October 1, 1939, we have had 8,107 hospital deliveries with 13 maternal deaths, a rate of 0.16 per cent, or 16 per 10,000 deliveries. We have performed 531 cesarean sections, an incidence of 6.5 per cent. Four cesarean deaths have occurred, a cesarean mortality rate of 0.75 per cent. Of the four cesarean deaths, one was an elective cesarean, making our elective cesarean mortality rate 0.18 per cent. All figures are uncorrected.

A careful study of recent statistics indicates that we do more cesarean operations in Stamford than are performed in most communities and in most teaching hospitals. I have endeavored to the best of my ability to determine whether or not we are justified in continuing our high cesarean rate based on our own results.

*Presented at a meeting of the Stamford Medical Society, Dec. 10, 1946.

ternal mortality will be improved. That the above is actually occurring in Stamford is shown in the above illustration. As examples of complicated vaginal deliveries I have chosen versions, high forceps, and midforceps. Since 1940 our cesarean rate has gradually increased from 4.3 per cent up to its present level of 7.8 per cent. With this increase, and most of the increase is in the elective cesarean group, versions have dropped from a high in 1941 of 1.4 per cent (twelve) to practically 0, there having been only two versions in the last three and one-half years. The high forceps rate in 1940 was 0.45 per cent (four); in 1943 the rate was 0.13 per cent (two), and there has not been a high forceps delivery since 1943, two and one-half years. The midforceps operation which carries about the same hazard to the mother as a cesarean, according to Irving, has dropped from a high in 1940 of 6.6 per cent to a low in 1945 of 1.6 per cent. I believe that the lessening of the complicated vaginal deliveries is at least in part due to the increase in elective cesareans.

Keeping in mind the above changes in our methods of caring for obstetric patients in Stamford during the last six and one-half years, let us inquire into our final maternal mortality. Our uncorrected maternal mortality in Stamford has been 0.16 per cent, or sixteen deaths per ten thousand deliveries, during this period. For the State of Connecticut as a whole between 1939 and 1943 the maternal mortality was 0.22 per cent, or twenty-two per ten thousand births. For the United States in 1942 the maternal mortality stood at 25 per ten thousand births. Chicago in 1944 reported a maternal mortality for the city of 16 per ten thousand births. Chicago Lying-in Hospital reported 17 per ten thousand births between 1931 and 1945. Waters from Margaret Hague Hospital reports a mortality of 29 per ten thousand between 1932 and 1943. The New York Lying-in Hospital reports 24 per ten thousand between 1932 and 1939.

I would now like to discuss each of our thirteen maternal deaths and ascertain their relation to the high incidence of cesarean sections. First, let us consider each of the four cesarean deaths.

CASE 1.—(3610) A 33-year-old white woman, para vi, gravida vii, had recently spent eleven months in a tuberculosis sanitarium. She became pregnant while she was still there. At the seventh month of pregnancy she had a profuse vaginal hemorrhage and was admitted within an hour. A diagnosis of tuberculosis and placenta previa was made. Because the hemorrhage was still uncontrolled at the end of two hours, and labor had not started, a cesarean operation was performed. We recovered a premature stillborn child; the vaginal hemorrhage promptly stopped and did not recur. The patient received plasma immediately after the operation, blood one and one-half hours post-operatively, then glucose. The plasma and glucose were repeated that same operative day. The following day she received more blood and glucose. At this point the hemoglobin was 32 per cent. Her course was progressively downhill and she died on her fifth postoperative day. There was no postoperative hemorrhage; her abdomen remained soft and there was very little fever until just before death. The patient repeatedly coughed up blood. It was felt the cause of death was irreversible shock from the blood loss, to which no doubt the operation contributed. I feel the chief criticism of the way this

tients, the cesarean mortality factor compares favorably with that of the other institutions mentioned in the table.

The above statistics have been chosen because each is from a well-known institution in a different part of the country, and all figures are relatively recent, none antedating 1931. Earlier figures are at such variance with more recent statistics that I do not feel they are helpful in determining present-day policies.

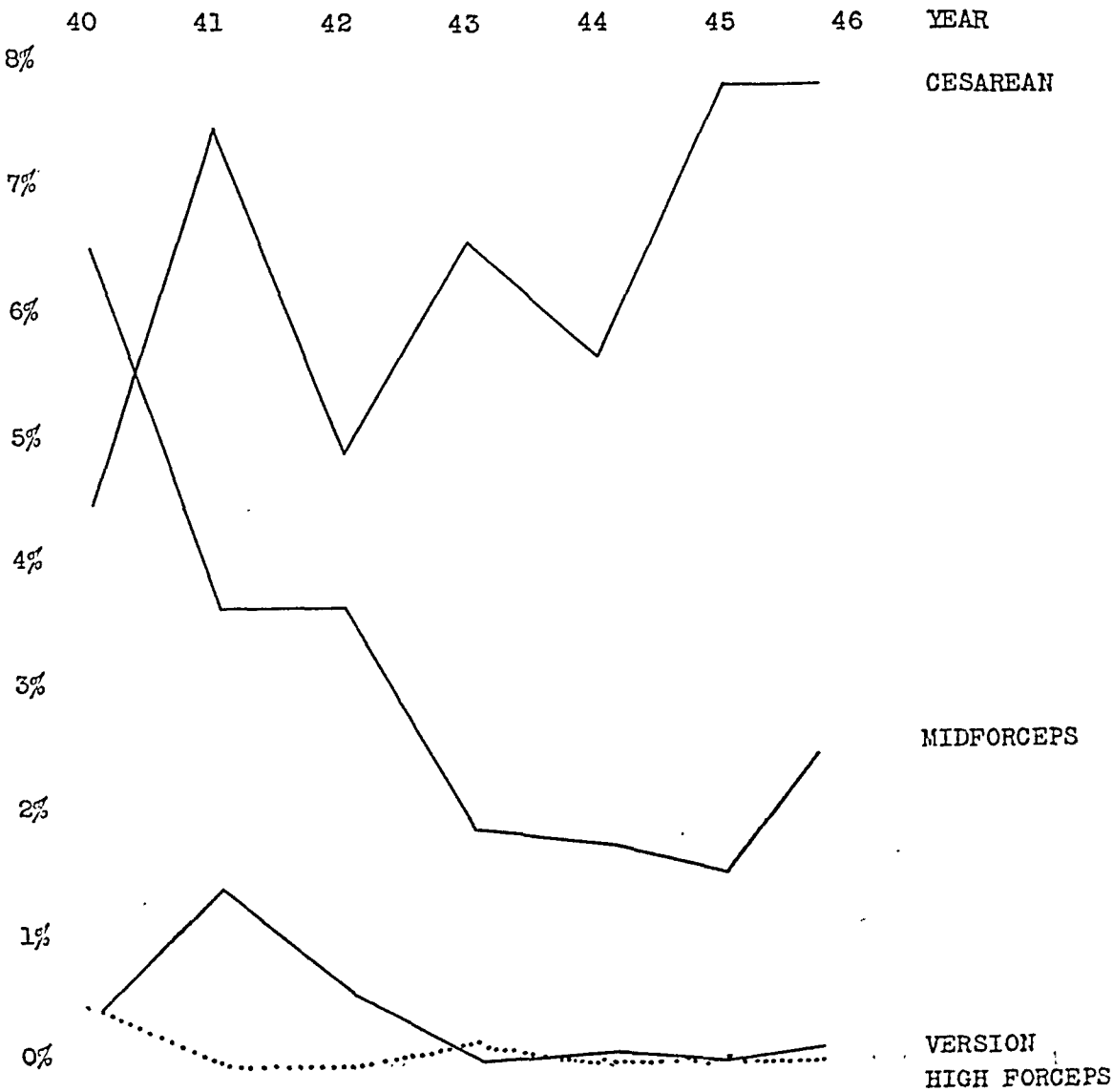


Fig. 1.—Percentage of annual cesareans, midforceps, versions, and high forceps, October, 1930, to July, 1946.

Even the cesarean mortality factor is only a partial answer to the over-all mortality picture. By doing more cesareans, especially the elective operation, one would expect a lessening of complicated vaginal deliveries. In our hospitals we have many more maternal deaths occurring from noncesarean patients than from the cesarean group. If the complicated vaginal deliveries can be lessened materially by doing more elective cesareans, I feel that our ultimate ma-

CASE 9.—(3499) The patient, aged 25 years, had a rheumatic history. This was her second delivery. The patient had a brief labor. She coughed excessively and died on her first postpartum day from "Exhaustion due to cardiac asthma and acute pulmonary edema."

CASE 10.—(495) The patient was 39 years of age, with rheumatic heart disease. The last three months of pregnancy were spent in bed because of heart failure and decompensation. She was delivered in bed because of cardiac condition. This was her tenth child, delivered spontaneously after a three-hour labor. She died on her third postpartum day from heart failure.

CASE 11.—(2139) A primipara, aged 38 years of seven months' gestation. She had several hemorrhages at home and was admitted in labor and bleeding. Diagnosis of premature separation was made. Following an eight-hour labor a version was done and the child was delivered. There was a postpartum hemorrhage and the patient died two hours after delivery. Here is a case where I believe a cesarean does enter the picture. A 38-year-old primipara with a premature separation in the opinion of some is handled in a safer fashion by prompt cesarean section than by an eight-hour labor and version.

CASE 12.—(93663) This patient, aged 28 years, was delivering her second child. Following a sixteen-hour trial labor, an attempt to deliver the child with high forceps failed. A version and extraction was performed with difficulty and the mother died one hour later. In this case I feel cesarean enters the picture. If so little progress has occurred after sixteen hours of labor that the head has barely engaged, and there is some reason for delivering the patient, cesarean is a safer procedure than either high forceps or version, or both.

CASE 13.—(104100) A primipara, aged 34 years, after thirty hours of trial labor the head was found to be in the midpelvis and not progressing. Delivery was attempted with midforceps and failed. A version and extraction was done with difficulty and a stillborn child obtained. The mother died about six hours later. Had we regarded this patient as an elderly primipara and done an elective cesarean I feel her prospects would have been better. Failing this, had we recognized that labor was progressing unusually slowly, and performed a cesarean after a short trial labor before vaginal instrumentation, her prospects would have been better.

Conclusions

1. A new term has been introduced, "cesarean mortality factor," which facilitates comparing and comprehending cesarean mortalities. The factor is the actual number of cesarean deaths to be expected for each ten thousand deliveries.

2. The cesarean rate in Stamford during the last six and one-half years has been 6.5 per cent, and is still rising.

3. Our cesarean mortality factor compares favorably with other institutions.

4. As our cesarean rate has constantly increased, our complicated vaginal deliveries have constantly decreased.

5. A careful study of our cesarean deaths does not indicate that another method of delivery would have saved many of these cases.

6. A careful study of our noncesarean deaths does indicate that some lives might have been saved by a more liberal interpretation of cesarean indications.

patient was handled was the delay in getting in adequate amounts of blood promptly. Her first transfusion was given one and one-half hours postoperatively, her second the next day, and her third on the fourth postoperative day. We had no blood bank at this time and it was difficult to get adequate amounts of proper blood promptly. We now have a blood bank. I feel we can say the cesarean contributed to this patient's death, but I do not feel it proper to say the cesarean caused this death.

CASE 2.—(105372) A 29-year-old woman with her first delivery had a fifty-hour trial labor, an attempted version, and an attempted forceps delivery. Finally a cesarean section was performed, followed by death on her fourth postoperative day from pelvic peritonitis. The criticism here is obvious: too long a trial of labor, a cesarean after contraindications had risen to a high point, failure to follow the cesarean with a hysterectomy. With this case I cannot blame the operation for the death, but rather the delay in doing the operation. A little less conservatism in the early part of this labor might well have given us one less maternal mortality.

CASE 3.—(114237) A 48-year-old white woman who had had a previous cesarean operation had an uneventful convalescence till her eighth postoperative day, when she had a pulmonary embolus and died within a few minutes. This represents our only elective cesarean death. The operation must be held responsible.

CASE 4.—(124819) A 25-year-old white woman with a slightly contracted pelvis was given a sixteen-hour trial labor. Her uterus was found to be in tonic contraction, and she died on her seventh postoperative day from paralytic ileus. This we must accept as a cesarean death after a reasonable trial of labor.

In reviewing these four cesarean deaths can we hold the frequency of our operations accountable? The patient in Case 1 did not receive adequate quantities of blood soon enough. With or without a cesarean, under these circumstances, probably the result would have been the same. In case 2, had the operation been performed more promptly rather than not at all, I feel the outcome would have been better. In Case 3, I feel the patient should have had a cesarean, and no other form of treatment would have increased her prospects for survival. The patient in Case 4 with a slightly contracted pelvis was given an adequate trial labor followed by section.

Now let us take up the noncesarean deaths.

CASE 5.—(123578) The patient was delivered at home three days before admission. She was admitted to the hospital on the medical service because of heart failure, and died from heart failure two days after admission.

CASE 6.—(120021) After a four and one-half hour labor, the patient was delivered by low forceps. No laceration resulted. The patient died on the twenty-eighth postpartum day from lobar pneumonia.

CASE 7.—(108589) The patient had a six and one-half hour labor and was delivered by low forceps. Shortly after this easy delivery, the patient went into shock. After a delay of some hours, the patient was found to have an inverted uterus which was replaced with difficulty. The patient died later the same day.

CASE 8.—(103355) An incomplete infected abortion had occurred between three and four months. The patient died from septicemia and peritonitis after eighteen days in the hospital.

MANAGEMENT OF POSTABORTAL PERITONITIS*

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AN ANALYSIS of the pathogenesis and associated pathologic findings in 61 fatal cases of postabortal peritonitis proved that the most common pathway of infection from the endometrium to the peritoneum was by direct extension through the tubes.¹ Infection of the peritoneum by way of the parametrium and myometrium was less frequent.

The medical treatment of postabortal peritonitis, exclusive of perforation, was wholly unsuccessful. Not one patient who was proved to have postabortal generalized peritonitis recovered. Baisch,² Latzko,³ Jesierski,⁴ and others have had similar experiences. Since 1941, the entire problem has been restudied, and selected cases of postabortal peritonitis have been treated with surgery.

Surgery must be preceded by accurate diagnosis. As a result of clinical experience correlated with postmortem studies, it has been found that abortion may be classified into six main groups.⁵

Type I.—Endometritis; the infection is limited to the cavity of the uterus and there is no evidence of extrauterine extension.

Type II.—Parametritis; cellulitis of the broad ligament. The infection has extended to the extraperitoneal supporting tissue of the uterus.

Type III.—Thrombophlebitis; the infection has extended to the uterine or ovarian veins. The thrombus may be fixed to the vein, or showers of infected emboli may be cast off.

Type IV.—General sepsis in which bacteria lights on the heart valves and are disseminated from this site.

Type V.—Generalized peritonitis.

Type VI.—Perforation of the uterus.

The usual signs and symptoms of generalized peritonitis are well known and need not be described. There are, however, some features of generalized peritonitis peculiar to postabortal disease which require clarification.

In patients who are seen at Harlem Hospital, the peritonitis is usually fulminating in nature, and death occurs rapidly. The majority of these patients have had induced abortions, many with the crudest instruments and lack of asepsis. In such cases the diagnosis is self-evident, and the problem is whether the patient, despite intensive supportive therapy, is able to withstand the further shock of surgery.

In a smaller, but not inconsiderable number of patients, a milder course may prevail, as in patients who lived from fourteen to forty-eight days after hospitalization. Localization of pus between the intestines, in the lumbar gutter, the pelvis, and subphrenic regions is common. On abdominal and vaginal

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7. Our ultimate maternal mortality of 16 per ten thousand births during the period of this study is commendable. I feel that our use of cesarean sections has contributed to this figure.

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peritonitis causes the mortality and morbidity rate to be lowered; thus a false impression is created with respect to the prognosis and efficacy of treatment.

The differential diagnosis of peritonitis secondary to perforation of the uterus is impossible except by accurate history or evident signs of perforation such as bowel or omentum projecting into the vagina or x-ray visualization of foreign bodies such as catheters in the abdominal cavity. If, as will be shown, early surgery is adopted as the guiding principle for all postabortal peritonitis, such differentiation is unnecessary.

Finally it should be clearly understood that the patients who are observed at Harlem Hospital are usually admitted in the late stage of peritonitis. Except for a sporadic case, the peritonitis is present on admission.

The duration of peritonitis preceding hospital admission is, of course, conjectural; however, the average history of bleeding in patients with postabortal peritonitis is ten days before admission to the hospital. The importance of this from a surgical viewpoint is that early surgery is rarely possible, a fact which will be more fully discussed later.

Therapy

It has been aptly said that the cure of puerperal fever is of secondary importance compared to its prevention. The sulfonamides and penicillin present a very great advance in the prevention and treatment of postabortal infection. It is well known that para-amino benzoic acid found in pus and necrotic tissue inhibits the chemotherapeutic action of the sulfonamides, thereby rendering them ineffective in the treatment of postabortal peritonitis. On the other hand, penicillin might seem *a priori* to furnish a cure. However, this has not proved to be so, since, notwithstanding these advances, from five to eight cases of generalized peritonitis, are still seen each year at Harlem Hospital. This incidence is identical with that prior to the chemotherapeutic era. Other forms of postabortal infection such as parametritis and blood stream sepsis have markedly diminished, but peritonitis is still seen in identical proportions. Why this should be so is not clear, but there is no doubt from our own statistics that this is a valid statement.

Hysterectomy for puerperal fever is thought to have been first performed by B. S. Schultz in 1886. Since that time there have been numerous reports of surgery for postabortal and puerperal peritonitis, particularly in the European literature. Unfortunately in many reports the etiology and extent of the peritonitis, as well as the exact details of operative management, are not made clear. In general, the German gynecologists have preferred incision and drainage of the peritoneum with or without the instillation of antiseptics into the abdominal cavity. Thus Latzko was able to obtain 24.2 per cent cures in 335 cases following abdominal incision and drainage. The best results were obtained when intervention was done within the first forty-eight hours of illness. Halban and Koehler⁶ stated that the recovery rate is 32 per cent if operation is performed within twelve hours. Thereafter the percentage diminished so that after seventy-two hours surgery is useless and death was inevitable in diffuse peritonitis. Koblanek⁷ reported 44 cases, of whom 20 per cent recovered. Jerserieski reported 75 cases of postabortal peritonitis; 28 were not operated upon, and all died. The remaining 47 were operated upon and 25 per cent recovered. Döderlein preferred vaginal drainage. Simon, of his clinic, reported 37 recoveries in 50 cases of colpotomy. This report includes.

examinations, these localized intraperitoneal abscesses may have been interpreted as parametric exudates until death; autopsy then shows a generalized peritonitis. However, since these masses are formed as a conglomeration of abscess, induration, distended bowel, and adherent omentum, their outline characteristically undergoes frequent change; *a pelvic or abdominal mass which undergoes daily variation in outline is considered to be pathognomic of this type of peritonitis*. In many such cases, it may seem as though the patient will finally recover. The abdomen may become soft, the mass disappears either spontaneously or through drainage, a hopeful prognosis is considered, and then the patient dies from chronic sepsis as determined by autopsy.

General peritonitis caused by a perforation of a parametric or tubo-ovarian abscess directly into the peritoneum is catastrophic, and fortunately rare. It may be recognized by the sudden appearance of shock, high fever, and signs of peritonitis in a previously comfortable patient with postabortal parametritis.

The diagnosis of associated thrombophlebitis is rarely made clinically. It has been found difficult to palpate thrombosed veins with any degree of certainty. The overwhelming clinical picture of peritonitis masks any local signs and, in the rare case in which metastatic emboli are found, the signs of pulmonary infection are often indistinguishable from the signs of terminal bronchopneumonia.

In the differential diagnosis, a history, or clinical evidence of recent pregnancy or abortion is essential for an accurate differentiation from other forms of peritonitis such as those caused by a perforated appendix, ruptured pyosalpinx, perforated peptic ulcer, etc. As a result of fear or ignorance, an incorrect history is often obtained. If vaginal bleeding is present, every effort to obtain an accurate history should be made, and the possibility of a postabortal infection as a cause of peritonitis must always be considered.

From a gynecologic point of view, the most important syndrome to be differentiated from postabortal peritonitis is parametritis with evidence of peritoneal irritation. Not unfrequently a patient with parametritis has peritoneal irritation as evidenced by tenderness, rigidity, and distention of the abdomen. The peritoneum covering the broad ligament appears lusterless, shaggy, and edematous. There is little increase in peritoneal fluid.

In such patients the signs of peritoneal irritation subside within twenty-four to forty-eight hours of expectant treatment. In early cases of parametritis, examination of the rectovaginal septum has proved to be of some aid. In these cases, a tongue-like thickening is frequently observed, whereas this is rare in the early stages of spreading peritonitis.

Although many gynecologists consider patients with parametritis and associated peritoneal edema as having peritonitis, involvement of the general peritoneal cavity does not exist. This is the type of case to which the term "peritonismus" could be applied. While a local pelvic peritonitis may be present, there is no evidence of spreading peritonitis, and the two must be clearly differentiated. The inclusion of such patients with those of generalized

TABLE I

| | NON- OPER- ATIVE | RESULTS | NUM- BER OF OPERA- TIONS | TYPE OF OPERATION | RESULTS |
|------|------------------------|----------|-----------------------------------|----------------------------|-------------|
| 1940 | 7 | All died | 1 | Supracervical hysterectomy | Recovered |
| 1941 | 5 | All died | 2 | Incision and drainage | 2 Deaths |
| 1942 | 4 | All died | 1 | Incision and drainage | 1 Death |
| 1943 | 3 | All died | 2 | Total hysterectomy | 2 Deaths |
| | | | 1 | Supracervical hysterectomy | Recovered |
| 1944 | 6 | All died | 2 | Supracervical hysterectomy | 2 Recovered |
| 1945 | 4 | All died | 2 | Supracervical hysterectomy | 1 Died |
| | | | 1 | Total hysterectomy | 1 Recovered |
| 1946 | 0 | 0 | 3 | Supracervical hysterectomy | 2 Recovered |
| | | | | | 1 Died |

pads. No attempt is made to break up any intestinal adhesions except those to the pelvic organs, and these are rarely an important or prominent feature. The intestines are walled off with three laparotomy pads, and the uterus, tubes, and ovaries clearly exposed. A routine supracervical hysterectomy and bilateral salpingo-oophorectomy is then performed. The tissues are markedly friable and suture-ligatures are usually preferable to clamps. After the uterus, tubes, and ovaries have been extirpated, the posterior cervix is grasped with two tenaculi and with a straight Mayo scissors, the entire thickness of the posterior cervix is incised down to the vagina. Caution to see that the rectum is not injured is obvious. As a result of this incision, the whole cervix is widely patulous. Hemostasis of the cervix is secured by a running lock stitch applied to the two cut edges of the cervix, extending from the internal os to the vagina.

From five to seven Penrose drains are then inserted through the bisected cervix to the peritoneum. Ten grams of sulfanilamide are dusted over the pelvic peritoneum and the sigmoid colon is carefully placed across the pelvis to exclude the general peritoneal cavity and minimize the possibilities of post-operative intestinal adhesion with obstruction. The abdomen is closed tightly in layers. The skin is drained with a small Penrose drain in the lower angle.

The reason for the choice of patients submitted to surgery is difficult to evaluate. Some patients were moribund upon admission. In two patients severe jaundice present on admission caused pardonable reluctance to institute surgery. These variable factors resulted in the division of cases into two groups; the first of 13 nonoperated cases with 100 per cent mortality and the second of 11 operated cases with 63 per cent recovery. Except for surgery, all received identical therapy so that the advent of chemotherapy in recent years cannot solely be responsible for the improvement in the reported results, although undoubtedly penicillin was of inestimable benefit in aiding recovery. Penicillin alone, even in fairly large doses, did not cure a single case. Recently Douglas¹² has reported a single case with recovery following large doses of penicillin and multiple incision and drainage of localized intra-abdominal abscess. It is our intention to employ much larger doses of penicillin and streptomycin than has hitherto been available. The last patient who was operated upon appeared to be moribund preoperatively. She was given 1,000,000 units of penicillin intravenously immediately on admission while awaiting preparation of the operating room and showed a dramatic clinical improvement. At the present time it cannot be said whether such heroic doses would be successful without the use of surgery.

however, "circumscribed pelvic peritonitis." Farrari, Houel, and Johier⁹ report four recoveries in five cases in which they performed a subtotal hysterectomy with ligation of the veins.

In the United States, surgery has not been widely used in postabortal peritonitis. Baldwin,¹⁰ however, has strongly advocated hysterectomy with or without ligation of the veins, a procedure which has largely been neglected. A total of 80 patients was operated upon, with a 25.5 per cent mortality. Of his last six patients all recovered. Polak¹¹ reported 15 cases—seven were incised and drained, with five deaths; eight were managed conservatively, with six deaths. He states "we have learned by bitter experience that puerperal and postabortal infective processes are actually extended by manual and instrumental manipulation."

In our own experience, medical treatment including sulfonamides and penicillin in varying dosages and routes of administrations, fluid balance, the use of small and large repeated transfusions, serums, vaccines, various nonspecific therapies, oxytocics, Wangenstein drainage, etc., have been of no avail and do not merit extended discussion. The first known case of recovery from postabortal peritonitis at Harlem Hospital was encountered in 1940. A patient mistakenly considered to be suffering from ectopic pregnancy was found to have an early spreading peritonitis. The uterus was somewhat enlarged, boggy, and the tubes inflamed. Uncertain of the exact pathology, a supracervical hysterectomy and bilateral salpingectomy was performed. On pathologic examination the uterus was found to contain infected placental tissue and the tubes to be the seat of a severe suppurative endosalpingitis. This patient made an uneventful recovery. Eight other cases of postabortal peritonitis observed in that year died under conservative management. It was then decided that henceforth surgery should be tentatively utilized, since the prognosis of suppurative peritonitis after abortion was inevitably fatal without operation.

In 1941 and 1942, 12 peritonitis cases were seen. In three, abdominal incision and drainage with the use of intraperitoneal ether and extensive drainage was employed; all three died, as did the nine nonoperative cases. In all, large amounts of sulfonamides were used. It was concluded that in the patients seen at Harlem Hospital the disease was of too long duration on admission for drainage alone to be effective.

It was then decided that hysterectomy should be done. Since that time, in the years of 1943, 1944, 1945, and the early months of 1946, 24 cases of peritonitis have been observed. Thirteen were not operated upon, but were given the most expert and attentive palliative therapy possible, which included frequent transfusions as well as large doses of sulfadiazine and, in 1945, large doses of penicillin as well. All 13 patients died. The remaining 11 patients had a total or subtotal hysterectomy performed; seven of these recovered, a recovery rate of 63 per cent.

The details of the 11 operative cases since 1943 are summarized in Table I. In 1943, two total abdominal hysterectomies were performed in which the pelvis was widely drained through the vault of the vagina. Both patients died. It was felt that the operating time could be shortened and the same results accomplished by supracervical hysterectomy, with splitting of the posterior lip of the cervix so as to permit wide drainage of the pelvis through the opened cervix by means of multiple Penrose drains. This routine has since been adopted.

The abdomen is opened through a left paramedian incision with the patient in moderate Trendelenburg position. A self-retaining retractor is inserted and the pus lying free in the peritoneal cavity is suctioned or soaked up with

2. Of three cases of postabortal peritonitis observed in 1941 and 1942, treated by incision and drainage of the peritoneal cavity in addition to intensive sulfathiazole therapy, all died. It is believed that the cases seen at Harlem Hospital are too far advanced for simple incision and drainage to be effective.

3. Since 1943, 24 cases of generalized postabortal peritonitis have been seen at Harlem Hospital. Thirteen were not operated upon and all died. Of 11 patients following hysterectomy, with splitting of the cervix and vaginal drainage, eight have survived.

4. From these findings, hysterectomy and bilateral salpingo-oophorectomy with splitting of the cervix and vaginal drainage in conjunction with appropriate chemotherapy, multiple blood transfusions, and intestinal drainage (Levin Tube, Wangenstein apparatus) is urged as the most effective therapy yet devised. For technical reasons, and to decrease shock, supracervical hysterectomy with splitting of the posterior lip of the cervix and the insertion of multiple drains into the pelvis is preferred to total hysterectomy. Vein ligation was not employed, and is not deemed an essential adjunct to surgery.

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In no case has vein ligation been done. From autopsy experience, it does not seem as though the type of thrombophlebitis which may accompany peritonitis is in itself responsible for generalized sepsis or major embolic phenomena. This is reflected clinically in the fact that repeated blood cultures in cases of peritonitis were positive in less than 3 per cent of all cases studied. Furthermore, sepsis from thrombophlebitis was not the cause of death in any of the patients who died.

In the discussion of Baldwin's work, two objections were repeatedly expressed. The first was the uncertainty of preoperative diagnosis, and the second the difficulty of the operative technique required. As to diagnosis, there can be little doubt that Baldwin did operate on many patients with parametritis and so-called thrombophlebitis as well as generalized peritonitis. There also can be little question that it is rare to see death ensue from parametritis. Careful medical therapy including cul-de-sac drainage when abscess ensues is invariably successful. Thrombophlebitis responds well to supportive and chemotherapy, and to date we have not had recourse to surgery in such cases. As a result of cumulative experience with a large abortion service in a municipal hospital, the diagnosis of these types of postabortal infection does not usually present great difficulties, and we believe that by careful analysis of each case, generalized peritonitis can be readily diagnosed preoperatively according to the criteria previously discussed.

Careful clinical observation permits an accurate diagnosis almost without exception. It is to be expected that a rare error in diagnosis will occur, but such an error seems negligible in relationship to the fatal course of the non-operative cases. The risk of laparotomy in such mistaken cases would not seem to be greater than that undertaken for a mistaken diagnosis of acute appendicitis. To date, such an error has been made on only one occasion. The abdomen was closed without further surgery, and her convalescence was uneventful.

Abdominal or cul-de-sac puncture for diagnosis has been considered, but the risk of false information and the dangers of its performance when distention is present has discouraged its use. It is stressed that the diagnosis of generalized peritonitis can be made with considerable certainty clinically, that such cases are invariably fatal and hysterectomy is reserved only for such cases in which this fatal outcome has been shown to be inevitable by experience.

Patients with spreading postabortal peritonitis as described herein are generally seen only on the service of large municipal hospitals and rarely if ever in private practice. Preventive measures in such patients are not possible since almost all are admitted after the onset of spreading peritonitis. Medical treatment including chemotherapy with the sulfonamides and penicillin alone have not resulted in any known cure to date. On the other hand, supracervical hysterectomy and bilateral salpingo-oöphorectomy with splitting of the cervix and drainage combined with penicillin has dramatically cured two-thirds of patients operated upon.

Summary

1. The management of spreading postabortal peritonitis exclusive of perforation of the uterus is discussed. If patients with localized pelvic peritonitis secondary to parametritis are not included in this group, all known patients with generalized peritonitis following abortion have died regardless of the type of medical therapy employed including the use of both sulfadiazine and penicillin.

TABLE I. CONDITIONS FOR WHICH OPERATION WAS PERFORMED.

| CONDITION | NO. CASES |
|-------------------------|-----------|
| Inflammatory disease | 110 |
| Endocervicitis | 30 |
| Benign ovarian tumors | 29 |
| Intractable bleeding | 28 |
| Prolapse | 27 |
| Lower abdominal pain | 20 |
| Endometriosis | 17 |
| Pelvic malignancy | 14 |
| Cystocele and rectocele | 7 |
| Ectopic pregnancy | 6 |
| Dysmenorrhea | 5 |
| Tuberculous salpingitis | 4 |
| Hematoma broad ligament | 1 |
| Cholelithiasis | 1 |
| No symptoms | 1 |

TABLE II. AGE INCIDENCE.

| AGE | NO. CASES |
|---------|-----------|
| 17-20 | 11 |
| 21-30 | 99 |
| 31-40 | 133 |
| 41-50 | 52 |
| Over 51 | 5 |

The average age was 34 years, the youngest, 17, the oldest, 61 years.

are young women, and every effort must be made to preserve their pelvic organs. It has been a common experience of the authors that if operation is delayed long enough in treating salpingitis it will often prove to be unnecessary. The temptation to "clean out" the pelvis in such cases is often strong and must be guarded against. Probably the most difficult decision to make is what to do with the tubo-ovarian abscess at operation. The ovary is usually not identifiable as such, and lies in the inflammatory and scar tissue at the base of the abscess cavity. A satisfactory result can be obtained by resecting the abscess wall and leaving the base of the cavity open and undisturbed. Such cases do not require drainage. Once the continuity of the abscess is broken the reparative processes of the body handle the remaining inflammatory tissue with amazing facility. The uterus should be freed of adhesions and suspended at the same time. The old excuse that if you take out the tubes you might as well take the uterus and ovaries too does not hold water. If the ovaries and uterus are preserved, these patients will continue to menstruate normally.

Endocervicitis.—Of the thirty cases subjected to panhysterectomy for cervicitis, two had an associated dysfunctional bleeding. The remaining twenty-eight presented no symptoms except those referable to the leucorrheal discharge. In the presence of a lesion in the uterine corpus, cervicitis may be a definite indication for panhysterectomy. In the absence of a lesion in the corpus, it is difficult for the authors to reconcile themselves to the idea that hysterectomy plays any part in the management of cervicitis. Cauterization, conization, and, if necessary, amputation are readily available and simple measures. Even if one feels that metaplasia, epidermization, or the so-called "Bowen's Disease" may be a forerunner of malignancy the simpler measures will just as adequately manage the lesion. In rare instances a questionable lesion is found which cannot be confirmed or denied by biopsy. In such cases the authors prefer careful

INDICATIONS FOR REMOVAL OF A NORMAL UTERUS

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IN THE ten-year period prior to August 1, 1946, there were 1,701 hysterectomy specimens received by the pathologic department of this institution. Of these, 300 were reported as normal. This report is the result of a critical review of these 300 cases, and represents an effort on our part to arrive at definite conclusions concerning removal of a normal uterus.

Comment

1. Conditions which may be considered definite indication for removal of a normal uterus are:

Malignancy.—The fourteen cases with pelvic malignancy are further broken down into eleven with carcinoma of the cervix and three with carcinoma of the ovary. The diagnosis of cervical malignancy had been made by biopsy. After a course of radiation therapy the uterus was removed and reported as normal. Radical surgery in the properly selected patient, in combination with radiation therapy, is definitely indicated in pelvic malignancy.

Tuberculous Salpingitis.—Previously undiagnosed tuberculous infection was found in four cases at operation, and the uterus was removed with the tubes as a matter of routine. That there was not an associated acid-fast endometritis found in these four cases is merely of academic interest. Certainly there was no way of proving it at operation.

Prolapse.—Vaginal hysterectomy for correction of prolapse in older women is an entirely acceptable procedure. In younger women there is no indication for it, and the Manchester-Fothergill operation or a uterus suspension should be performed instead. There were two patients in this group of twenty-seven cases upon whom hysterectomy should not have been performed. Their ages were 22 and 24 years respectively, and neither had any complaints referable to the uterus other than those produced by the prolapse.

Intractable Bleeding in Older Women.—Of the 28 cases of persistent uterine bleeding, ten were in older multiparas for whom repeated curettements and medical measures had failed to provide relief. Four cases occurred in women past the menopause, making a total of fourteen such cases. In this type patient hysterectomy may be definitely indicated. The authors prefer to employ a small dose of intrauterine radium to check the bleeding without subjecting the patient to a major operation.

2. Conditions which may be considered questionable indications for removal of a normal uterus are:

Inflammatory Disease.—The 110 cases with inflammatory disease of the adnexa are further broken down as follows:

| | |
|----------------------|----|
| Acute salpingitis | 1 |
| Subacute salpingitis | 21 |
| Chronic salpingitis | 76 |
| Tubo-ovarian abscess | 12 |

Surgery in the acute stages of this disease is definitely not indicated. In the chronic group corrective measures are often necessary. Most of these patients

the upper abdominal incision, made a lower abdominal incision, and removed a normal uterus with normal tubes and ovaries.

No Symptoms.—This patient was a 40-year-old woman who reported to a birth control clinic to be fitted with a diaphragm. She had no complaints and her menstrual history had always been normal. There was no excess bleeding or discharge. At the clinic she was told by the examining doctor there was a possibility she might have a tumor of the womb and she was referred to a gynecologist. The latter advised the patient that an operation would be necessary. At operation a normal uterus was found and removed.

Conclusions

1. Pelvic malignancy, tuberculous salpingitis, prolapse, and intractable bleeding in older women may be definite indications for removal of a normal uterus.

2. Inflammatory disease, endometriosis, benign ovarian tumors, dysfunctional bleeding in younger women, and endocervicitis are at best questionable indications for removal of a normal uterus.

3. Ectopic pregnancy, cystocele and rectocele per se, psychoneurosis, and dysmenorrhea are not indications for removal of a normal uterus.

4. In this series of 300 operations there was no indication for hysterectomy in 43 cases, or 14 per cent, and questionable indication in 197 cases, or 65.6 per cent.

5. The authors conclude that even in a well-supervised teaching hospital hysterectomies are sometimes performed with little or no justification for the operation.

observation of the lesion, multiple biopsies, and, if necessary, amputation of the cervix with study by serial section before instituting more radical measures.

Benign Ovarian Tumors.—These thirty cases are further broken down as follows:

| | |
|--------------------------------------|----|
| Simple serous cyst (Exceeding 5 cm.) | 12 |
| Dermoid and teratoma | 10 |
| Large benign cystomas | 7 |
| Fibroma | 1 |

With a large tumor completely distorting the pelvic structures in an older woman, hysterectomy may be indicated to facilitate the operation. In younger women every effort must be made to preserve the other ovary and the uterus. On occasions, the preservation of a small strip of ovarian tissue on one side only along with the uterus will prevent an artificial menopause. Special attention must be directed to the small follicle cysts and hematomas which result from normal cyclic activity of the ovary. These structures are not abnormalities, yet they are frequently mistaken for pathologic lesions by surgeons and removed. To add the insult of removing a normal uterus to such a procedure should constitute malpractice.

Endometriosis.—In this condition it is the opinion of the authors that removal of a normal uterus or ovaries is not indicated. These patients often do surprisingly well with simple removal of the endometriomata or their partial excision. If necessary, x-ray castration will check the progression of the lesion promptly.

Intractable Bleeding in Young Women.—In these cases hysterectomy represents surrender on the part of the physician to the demands of the patient and her relatives to "do something" to stop the bleeding. This type of case can be most trying to the gynecologist's patience and judgment. In this group falls the youngest patient in this study, a girl 17 years of age.

Hematoma of the Broad Ligament.—This one patient developed a pelvic mass the size of a volleyball subsequent to a curettement. After two months of observation it showed no evidence of subsiding and laparotomy was performed. At operation the pelvic structures were found to be so distorted that hysterectomy was considered advisable.

3. Conditions which are not indication for removal of a normal uterus are:

Lower Abdominal Pain and Dysmenorrhea.—These twenty-five cases are an excellent illustration of what may happen to psychoneurotic women if they pester their doctor long enough. Most psychoneurotics with abdominal complaints manage to get themselves operated upon at least once, but the surgeon who removes more than an appendix in such cases is overzealous, to say the least.

Cystocele and Rectocele.—The seven cases with this complaint alone had no appreciable degree of descensus and no symptoms referable to the uterus. All had a repair of the cystocele and rectocele from below, combined with an abdominal supravaginal hysterectomy. In none was there clear indication for laparotomy, let alone hysterectomy.

Ectopic Pregnancy.—Of these six cases, four were ruptured tubal, one a tubal abortion, and one ruptured ovarian. To add the shock of hysterectomy to a patient already or potentially in shock cannot be considered anything but sheer foolhardiness.

Colelithiasis.—This one case was of a 42-year-old woman whose only complaint was upper abdominal pain produced by gall stones. After cholecystectomy the surgeon thought he detected an enlarged ovary by palpation. He closed

Early rising in this series of cases should be defined as controlled ambulation. The patients are encouraged to walk to the bathroom instead of using bed pans, and to remain out of bed for short intervals only. No changes in technique were instituted in any of these patients. Episiotomy repairs were all routinely performed with No. 0000 chromic catgut as described by Waters.² Cesarean operations were all performed through low transverse abdominal incisions, except where a previous midline incision existed; the fascia was sewed with double No. 0 chromic catgut suture.

All patients requiring catheterization were catheterized at least one time for residual urine after voiding had begun, and if this amount was above 50 c.c., catheterization was repeated after each voiding until the amount of residual urine was less than 50 c.c. Patients who voided apparently normal amounts of urine without difficulty and at normal intervals were not catheterized at all. The estimations as to the amount of lochia or postpartum bleeding were made from our observation at our daily rounds at the hospital, in addition to the reports of the obstetric nurses in attendance.

Analysis of Statistics

This study is not intended to represent a comparative analysis of the three groups of puerperal women according to their time of rising. As may be seen in Table I, a much higher percentage of cesarean sections fall into the intermediate and the late risers than do in our early risers. This is because any of the patients who were more seriously ill or had more bleeding were not al-

TABLE I. STATISTICS

| | | | | |
|---------------------------------|-----|-------|-------|--|
| Total number of cases in series | 601 | | | |
| Total cesarean sections | 58 | | 9.6% | |
| Early risers | 490 | | 81.6% | |
| Vaginal deliveries | 451 | 92.0% | | |
| Cesarean sections | 39 | 8.0% | | |
| Intermediate risers | 93 | | 15.4% | |
| Vaginal deliveries | 77 | 82.8% | | |
| Cesarean sections | 16 | 17.2% | | |
| Late risers | 18 | | 3.0% | |
| Vaginal deliveries | 15 | 83.4% | | |
| Cesarean sections | 3 | 16.6% | | |

TABLE II. BLADDER FUNCTION

| Number of patients requiring catheterization after getting up | | | | | 31 | |
|---|--------|----------|--------------|----------|--------|----------|
| Number of patients not requiring catheterization after getting up | | | | | 570 | |
| | EARLY | | INTERMEDIATE | | LATE | |
| | NUMBER | PER CENT | NUMBER | PER CENT | NUMBER | PER CENT |
| Number studied | 490 | | 93 | | 18 | |
| Number of patients requiring catheterization | 167 | 34.1% | 32 | 34.4% | 8 | 44.4% |
| Number of patients not requiring catheterization | 323 | 65.9% | 61 | 65.6% | 10 | 55.6% |
| Total number of catheterizations | 435 | | 66 | | 12 | |
| Average number of catheterizations per patient | .88 | | .71 | | .66 | |
| Voiding complete on first postpartum day | 453 | 92.4% | 87 | 93.6% | 16 | 88.9% |
| Voiding not complete on first postpartum day | 37 | 7.6% | 6 | 6.4% | 2 | 11.1% |
| Clinical urinary infections | 11 | 2.2% | 3 | 3.2% | 0 | 0 |
| Gross morbidity | 15 | 3.0% | 7 | 7.5% | 5 | 27.7% |

FURTHER STUDIES IN EARLY PUERPERAL RISING

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IN NOVEMBER, 1945, we reported a series of 582 obstetric patients comprising a study in early puerperal rising,¹ pointing out that this practice goes back to ancient times and is not particularly an outgrowth of the recent shortage of hospital beds. The analyses of our data from that study yielded the following conclusions:

1. Delivered women can safely get up early in the puerperium with no harmful results occurring.
2. Bowel function is improved as a result of early puerperal rising.
3. Early puerperal rising reduces the amount of nursing care required.
4. The majority of patients subjected to early puerperal rising reported favorably on the method.
5. The patients getting up on the third or fourth postpartum day showed no advantages over those patients getting up on the first or second postpartum day.
6. It was our opinion that early puerperal rising resulted in a more rapid and comfortable convalescence, with less asthenia and less postpartum and postoperative depression.

At the time of the above report it was our hope that further study would result. Since that publication appeared, there has been generally a greatly renewed interest in the subject of early surgical and early puerperal rising. There have been many editorials and symposia on the "use and abuse of bed rest" as well as articles in popular magazines which have resulted in a strong public interest in early rising. We have now found that our patients exhibit a far greater knowledge concerning the subject, and we have also noted a definite change in their attitude toward the practice of early rising, whereas previously there was skepticism, there is now eager expectancy. Doctors practicing at the Cedars of Lebanon Hospital who do not allow their patients out of bed early have reported opposition from both their surgical and obstetric patients who believe early rising beneficial. All of this leads to the belief that early puerperal rising is gaining in favor with both the medical profession and the laity.

Method of Study

As in our previous study our cases were divided as follows:

1. Early risers: Ambulatory on the first or second postpartum day.*
2. Intermediate risers: Ambulatory on the third or fourth postpartum day.
3. Late risers: Ambulatory later than the fourth postpartum day.

*At Cedars of Lebanon Hospital, the first postpartum day is defined as "the day following delivery."

definitely improved with many more patients not requiring enemas. Since there were no cases of thromboses or embolism in our total observed series which now comprise 1,183 patients, we are again unable to confirm the reports of other authors that early puerperal and early surgical rising safeguards against these serious accidents. It is notable that we have not had a single case of episiotomy or wound breakdown in our present series of 601, and only one instance of skin separation in our previous series of 582 patients. Our observations do not lead us to believe there is any greater amount of postpartum bleeding, a point mentioned by Hanley.³

The postpartum studies reveal that of 721 early risers in our combined series 160 patients, or 22.2 per cent, had a midposition or retroversion of the uterus, while of 244 late risers in our combined series 59, or 24.2 per cent, presented this same finding, not too dissimilar percentages. It appears, therefore, that the belief that early puerperal rising may cause more retroversions of the uterus is unfounded. We have seen no cases of uterine prolapsus in any of our early risers, and we agree entirely with the belief of Guerriero⁴ that prolapsus is due to trauma at delivery.

Conclusions

We have presented a series of 601 delivered women, of which 490, or 81 per cent, were made ambulatory on the first or second postpartum day. Together with our previous series of 582 cases, this comprises 1,183 patients studied, of which 737 patients comprise the group of early risers. We believe that our earlier conclusions as enumerated at the beginning of this paper are further substantiated. We believe that the practice of early puerperal rising is gaining favor with the medical profession and with the laity. We intend to continue this practice and believe that time will prove its correctness.

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TABLE III. MISCELLANEOUS OBSERVATIONS

| | EARLY | | INTERMEDIATE | | LATE | |
|-------------------------|--------|----------|--------------|----------|--------|----------|
| | NUMBER | PER CENT | NUMBER | PER CENT | NUMBER | PER CENT |
| Lochia | | | | | | |
| normal | 485 | 99% | 92 | 99% | 16 | 89% |
| excessive | 5 | 1% | 1 | 1% | 2 | 11% |
| Perineal healing | | | | | | |
| good | 451 | 100% | 77 | 100% | 15 | 100% |
| fair | 0 | | 0 | | 0 | |
| poor | 0 | | 0 | | 0 | |
| Abdominal wound healing | | | | | | |
| good | 39 | 100% | 16 | 100% | 3 | 100% |
| fair | 0 | | 0 | | 0 | |
| poor | 0 | | 0 | | 0 | |
| Involution of uterus | | | | | | |
| good | 483 | 98.6% | 92 | 99% | 17 | 94.4% |
| fair | 4 | .8% | 0 | | 0 | |
| poor | 3 | .6% | 1 | 1% | 1 | 5.6% |
| Bowel function | | | | | | |
| moved spontaneously | 88 | 18% | 10 | 10.7% | 1 | 5.6% |
| enema required | 402 | 82% | 83 | 89.3% | 17 | 94.4% |
| Thrombosis | 0 | | 0 | | 0 | |
| Embolism | 0 | | 0 | | 0 | |
| All other complications | | | | | | |
| wound drainage | 0 | .0 | 1 | 1% | 0 | .0 |
| psychosis | 1 | .2% | 0 | .0 | 0 | .0 |
| respiratory infection | 1 | .2% | 0 | .0 | 2 | 11% |
| toxemia | 2 | .4% | 2 | 2% | 0 | .0 |
| mastitis | 1 | .2% | 1 | .0 | 0 | .0 |
| third degree laceration | 0 | .0 | 1 | 1% | 0 | .0 |
| cystitis | 11 | 2.2% | 3 | 3% | 0 | .0 |

TABLE IV. POSTPARTUM STUDIES

| | EARLY | | INTERMEDIATE | | LATE | |
|---|--------|----------|--------------|----------|--------|----------|
| | NUMBER | PER CENT | NUMBER | PER CENT | NUMBER | PER CENT |
| Number of patients studied | 477 | 100% | 88 | 100% | 18 | 100% |
| Excessive bleeding during first month post partum | 2 | .4% | 0 | 0 | 1 | 5.5% |
| Perineal healing | | | | | | |
| good | 477 | 100% | 88 | 100% | 18 | 100% |
| poor | 0 | 0 | 0 | 0 | 0 | 0 |
| Position of uterus | | | | | | |
| anterior | 387 | 81% | 70 | 79.5% | 14 | 77% |
| mid | 31 | 6.5% | 6 | 6.8% | 2 | 11% |
| retroverted | 59 | 12.3% | 12 | 13.6% | 2 | 11% |

TABLE V. CESAREAN SECTIONS

| | | | | | | |
|------------------|----|------|----|-----|---|-------|
| Number in series | 39 | | 16 | | 3 | 16.6% |
| Morbidity | 3 | 7.7% | 4 | 25% | 2 | 11.0% |
| pyelitis | 1 | 2.5% | 1 | 6% | 0 | 0 |
| parametritis | 2 | 5.1% | 3 | 18% | 1 | 5.5% |
| peritonitis | 0 | 0 | 0 | 0 | 1 | 5.5% |

lowed up as early as the more normal ones. For this reason also the higher morbidity figures in the intermediate and late groups are not significant. However, we feel that it does demonstrate that 490 out of 601 delivered women, or 81 per cent, could be made ambulatory on the first or second postpartum day with obvious benefit.

As in our previous study, we do not feel that the statistics demonstrate any obvious advantage as concerns bladder function. Bowel function seems

palpable, but increased in size to 10 by 12 cm., and was now palpable in the left lower quadrant, 6 centimeters above the symphysis. The mass was somewhat tender.

On June 22 examination under anesthesia confirmed the above findings. The uterus was anterior, consistent with a negative parous, nonpregnant uterus. A smooth, regular, fairly soft, rounded, movable mass approximately 8 cm. in diameter was felt deep in the left vault, which seemed compressible as though it were cystic. The right vault was negative. At a curettage, the uterine cavity was three inches deep, smooth and symmetrical, and yielded a moderate amount of grossly negative endometrium. A laparotomy performed with a preoperative diagnosis of ovarian tumor revealed no blood in the peritoneal cavity. There was, however, one filmy omental adhesion to the left anterolateral parietal peritoneum at which point there was some soft gray-brown material consistent with old blood undergoing organization. A biopsy of this area was taken. The left ovary was enlarged to approximately 7 cm. in diameter, consisting of dark brown hemorrhagic tissue and old blood clot. It was loosely adherent to the posterior parietes of the pelvis. Little or no normal ovarian tissue was left. The right ovary was normal except for a rather large (approximately 2 cm.) corpus luteum, which was biopsied. Both tubes were negative except that the left tube was loosely adherent to the ovarian mass by fibrin and organizing inflammatory exudate. The uterus was consistent with a negative parous nonpregnant uterus.

A left oophorectomy was performed and a grossly negative appendix removed. The patient had an uneventful postoperative course and was discharged on the ninth day. At her six weeks' postoperative visit she had been entirely well, having had an apparently normal catamenia from July 30 to August 4. Pelvic examination was negative.

Pathologic Examination.—*Gross:* The material consisted of the left ovary, biopsy from right ovary, endometrial curettings, biopsy from left anterior peritoneal wall, and appendix.

The left ovary (Fig. 1) measured 6 by 5 centimeters. The upper portion was dark reddish-brown in color. There were several small dark-colored areas over the rest of the ovary which appeared to be cysts containing old blood. The largest was 1½ centimeters in diameter. There was a denuded area one centimeter wide and two centimeters long across the upper lateral surface of the ovary, one centimeter from the hilum, where the ovary was separated from the left tube. The underlying ovarian stroma was very friable and infiltrated with old and recent hemorrhage. Upon cutting down through this area a thin white membrane was exposed behind which thin bloody fluid could be seen. Upon opening it, it was found to contain an embryo whose crown rump length was 16 millimeters. It was attached to the wall of the cavity by a fusiform cord 4 millimeters in diameter. The fetus showed brownish discoloration and slight maceration of the skin. The lining membrane of the cavity, which was 2½ centimeters in diameter, bulged in on all sides due to the large amount of hemorrhage between it and the surrounding ovarian tissue. Section through the largest of the dark colored raised areas on the surface of the ovary showed it to be a cystic structure filled with organizing blood.

The biopsy from the right ovary had the characteristic thick yellow convoluted wall and hemorrhagic center of a mature corpus luteum.

The biopsy from the left anterior peritoneal wall measured 2 by 3 by 4 millimeters, and was composed of fat and old blood clot.

The endometrial curettings measured 5 by 4 by 7 millimeters.

Microscopic.—Sections from the wall of the left ovary extending into the cavity of the ovisac showed it to be lined with a layer of somewhat flattened cells with deep-staining nuclei and cytoplasm characteristic of the amnion. The

PRIMARY OVARIAN PREGNANCY

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PRIMARY ovarian pregnancy occurs approximately once in 25,000 pregnancies.³ The total number of cases reported has been estimated from forty-four to two hundred.^{5, 6} The incidence of its occurrence in ectopic pregnancy is again variously reported from 0.7 to 1.07 per cent.¹⁻⁴ If all hemorrhagic lesions of the ovary, such as ruptured follicles, corpora lutea cysts, "chocolate cysts," and hematomas were given routine histologic examination, the number of ovarian pregnancies recognized would be greatly increased.^{6, 7} One hundred ten cases of ectopic pregnancy have occurred at the Free Hospital for Women, Brookline, Mass.; of this number the following is the only case thought to be primary in the ovary. Our incidence of this condition is therefore 0.9 per cent.

Mrs. N. M. C., a 24-year-old white housewife, married three years, was perfectly well until March 16, 1946, which was two months before her first visit to the Out-Patient Department and three and one-fourth months before operation; when, after carrying a baby carriage up two flights of stairs, she suddenly felt weak, faint, and dizzy. Shortly afterward she had sudden sharp, severe lower abdominal pain. Palpation of the abdomen by her family doctor, who arrived within the hour, was not painful. Her pain subsided soon and the next day she felt well except for tiredness and a "pulling" sensation in the lower abdomen when she sat erect. That night, she noticed that her navel protruded and was "black and blue," changing to yellow and then resuming its normal color in the course of a week. On the third day she resumed her household duties. She had noted no irregularity or change in character in her menses, her last menstrual period having occurred at its expected time, beginning approximately two weeks before the above episode.

During the next three months, she remained asymptomatic except that on intercourse she occasionally noticed deep pelvic pain never experienced previously. There was also some irregular bleeding consisting of six episodes, the first four at approximately two-week intervals, the last two at three-week intervals; each flow resembling her usual catamenia in duration, amount, and character. These were accompanied by a sense of "fulness" in the pelvis, relieved by the onset of bleeding.

Past medical history was negative except for occasional attacks of "bronchial asthma"; surgical history was negative. The patient had had one child, a full-term, normal delivery, eighteen months prior to entry; there had been no miscarriages.

At her first visit to the Out-Patient Department on May 14, the abdomen was soft, without tenderness or masses; the uterus anterior, small, firm, and movable without pain. The cervix showed a mild circumoral erosion one centimeter in diameter. Deep in the left vault there was felt a tender mass measuring 4 by 5 cm., which was thought to be consistent with a simple cyst. The cervix was biopsied, and she was given an appointment to return in one week. Three weeks later, on June 4, the mass in the left vault was still

thelium, part of which showed beginning degeneration. It was surrounded with a loose, fibroblastic stroma containing large pale nuclei, capillaries, and hemosiderin.

The section from the right ovary showed the cortex to contain many primordial follicles and part of a large corpus luteum (Fig. 3). The central core of the latter consisted of extravasated blood, numerous fibroblasts and some capillaries containing blood. The lutein cells next to the core showed many vacuoles in their cytoplasm. Many of the cells had deep-staining, finely vacuolated cytoplasm with pyknotic nuclei. The capillaries were straight, and most



Fig. 2.—Section from inner wall of cavity within the ovary showing invasion of ovarian stroma by chorionic villi and syncytial giant cells.

were collapsed and empty. There was no extravasated blood. There was an abundant supply of blood-filled capillaries in the columns of the theca interna together with a considerable amount of free, pink, granular secretion. The theca interna cells were large and granular, with large vesicular nuclei containing prominent nucleoli and occasional mitoses. The corpus luteum was active and approximately nine days old,³¹ which was consistent with the endometrium.

The endometrial curettings (Fig. 4) showed the surface to be undulating and covered with a layer of tall thick columnar cells. The stroma cells immediately beneath the surface and around the spiral arterioles were becoming vesicular and were acquiring more cytoplasm. A few mitoses were seen. The rest of the stroma was loose and moderately edematous. The glands were tortu-

stroma of the amnion was replaced by a wide zone of disintegrating red blood cells scattered among which were a few degenerated cell nuclei and the hyalinized borders of "ghost" villi. Beyond this area there were numerous chorionic villi undergoing various stages of necrosis (Fig. 2). Some were almost entirely hyalinized with a loss of cellular structure, others had undergone fibrosis. A few were seen in which the trophoblast showed only early necrosis and the stroma of the villi contained fetal blood vessels filled with blood. The Hofbauer cells were present in relatively large numbers.



Fig. 1.—The ovary opened to show the embryo and ovisac within the center of the ovary. (Suture material shown in closing areas sectioned while trying to locate the corpus luteum of pregnancy.)

Syncytial giant cells showing vacuolization and granular degeneration of both the cytoplasm and nuclei had invaded the ovarian stroma. The latter was heavily infiltrated with red blood cells, round cells, plasma cells, and large macrophages laden with hemosiderin. There were areas containing large pale polygonal cells showing decidual reaction, most of which were showing signs of degeneration. Numerous primordial follicles lined with flattened spindle shape epithelial cells surrounding well preserved ova were seen in the cortex. In early follicles, lined with a more fully developed layer of granulosa cells, the ova had disintegrated. The theca cells of the large atretic follicles had large vesicular nuclei and more abundant cytoplasm simulating a lutein reaction. An old follicular cyst was present whose cavity was filled with degenerated red blood cells and fibroblasts. On the surface of the ovary was a vascularized adhesion which contained an inclusion cyst lined with germinal epi-

developed in its own follicle or at some other site within the ovary. The corpus luteum of pregnancy had degenerated so much it could not be located by multiple sections of ovary containing the fetus. The biopsy of the only grossly recognizable corpus luteum in the opposite ovary corresponded in age to the current twenty-four day secretory endometrium.

The length of the fetus was consistent with an age of seven weeks according to the tables of Streeter.⁸ The vaginal bleeding episodes of the next two months can best be explained on a basis of "teetering" estrogen-progesterone



Fig. 4.—A section of the endometrial curettings showing the beginning predecidual reaction around the spiral arterioles and the dilated secretory glands with moderate serration of the lining epithelium and secretion within the lumina.

hormone levels in the presence of degenerating trophoblast⁹; the latter having finally lost its ability to inhibit the development of a new follicle with subsequent ovulation and the development of a twenty-four day secretory endometrium. It is evident from a review of the reported cases¹⁻³⁰ that endometrial curettings reveal a wide variation in both proliferative and secretory types, with a decidual reaction present only occasionally. This tends to support Kline's¹⁰ statement that the decidual reaction is not constant and that vaginal bleeding depends on changes other than the casting off of uterine decidua. It has long been known that the uterine curettings are of doubtful value in the diagnosis of extrauterine pregnancy. The etiology of this case, whether due to fertilization of the ovum within its follicle, or subsequent implantation in the same or the other ovary, cannot be stated.

ous and showed slight serration when cut longitudinally. Their epithelium was low columnar with basal ovoid nuclei and no mitoses. The lumina contained small amounts of secretion. The endometrium was secretory type in the twenty-fourth day of the cycle using the criteria set forth by Hertig³² for diagnosing endometrial biopsies.

The section from the anterior peritoneal wall consisted of a mass of hemosiderin and fibrin in which there were numerous small capillaries, plasma cells, round cells, and fibroblasts.

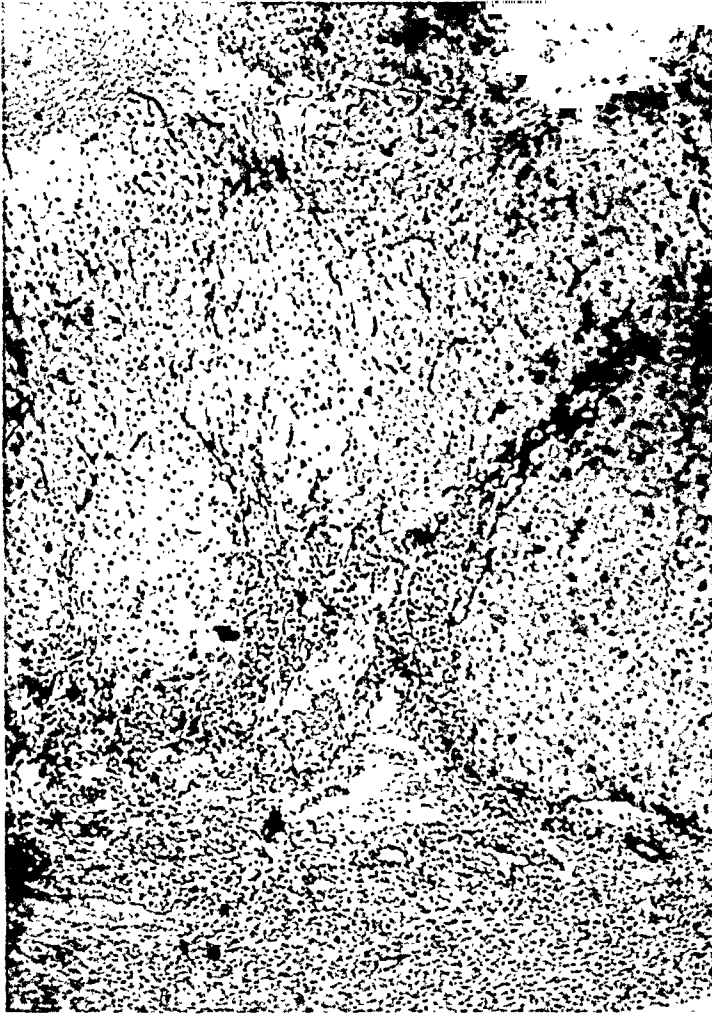


Fig. 3.—Section of active corpus luteum showing the straight capillaries among the lutein cells and the blood-filled capillaries and free secretion among the cells of the theca interna.

Discussion

The eventual fate of this conception, had it not been removed, is a matter of conjecture. All active growth processes and bleeding had ceased. Organization and resorption were under way, and eventual mumification and lithopedion formation might have occurred, as in the case reported by Norton and Alter.¹¹

In many cases, there is often a measure of doubt whether or not the ovary is the primary or secondary site of implantation. However, since both Fallopian tubes were intact and grossly normal, this case is thought to be a primary ovarian pregnancy. It cannot be determined whether or not the ovum

COEXISTENT CARCINOMA AND SARCOMA OF THE UTERUS*

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A TYPE of case which is considered rare is that of coexistent carcinoma and sarcoma of the uterus. According to Newell, only twenty similar cases had been reported prior to 1928—not so long ago. Oscar Frankl reported eight cases which were observed and studied in great detail over a period of fifteen years. He stated that it was possible for both carcinoma and sarcoma to exist in the same uterus, either closely approximated or distinctly apart. He studied the pathology of these tumors very carefully, recognized the fact that an accurate diagnosis was sometimes extremely difficult, and urged that a definite terminology be used in describing them. He suggested that the term sarcoma plus carcinoma be applied to separate tumors, carcinosarcoma to mixed tumors in which sarcoma and carcinoma are intimately mixed, and carcinoma sarcomatodes to a carcinoma which has characteristics of growth of sarcoma.

Virchow applied to all three groups the name carcinoma sarcomatodes, since he considered them to be true mixed tumors in which both epithelium and connective tissue were represented in the neoplastic growth. Herxheimer, in discussing the pathology of sarcoma and carcinoma in the same uterus, suggested three possibilities: (a) that carcinoma and sarcoma may develop simultaneously as the result of the same cause acting in different tissues; (b) that the atypical proliferation of epithelium on the base of a pre-existing sarcoma may lead to the development of a carcinoma within a sarcoma; and (c) that the stroma of a carcinoma may undergo a sarcomatous change. Ewing, in a consideration of the same subject, listed the following possibilities: (a) the simultaneous occurrence of two separate tumors which may invade one another; (b) the development of carcinoma at the point where a submucous or mural sarcoma meets the epithelial layer; and (c) carcinomatous changes in the glands of a sarcomatous or inflammatory polyp.

Most of the cases reported in the literature were either adenocarcinomas of the body and cervix or sarcomas arising from either the endometrium or myometrium, but not sarcomas arising in a myoma. It is obvious that an accurate diagnosis is difficult when the two neoplasms originate in the interior of the uterine cavity and encroach upon each other in such a way that the cells often lose their characteristics.

Carcinoma sarcomatodes of the uterus is the term used to designate a single neoplasm having the morphologic features of both carcinoma and sarcoma. Only seven cases of this type are reported in the literature. Carcinoma sarcomatodes has no characteristic clinical features. It is said to occur mostly in nulliparous patients after the menopause. Bleeding is a constant symptom and appears to be more persistent and profuse than in cases of carcinoma of the fundus of the uterus.

Goldstine reported a case of sarcoma and adenocarcinoma of the body of the uterus and adenocarcinoma of the cervix. The two large masses protruding from the fundus were covered by a markedly thickened endometrium.

*Read before the Section of Obstetrics and Gynecology, New York Academy of Medicine at its meeting January 28, 1947.

There is no evidence that sterility which is cited by Kuzma and Lillie¹² as a factor, played any part in this case. Endometriosis was not present, which is in contrast to some cases reported by others.¹¹⁻¹⁴ In view of the almost universal occurrence of endometrial stroma beneath the surface of the ovary which is transformed into pseudodecidua by the stimulus of pregnancy, it is possible that a fertilized ovum which was mechanically delayed in passing to the uterus might cause by its continued proximity to cells originating in the Müllerian system, a sufficient pseudodecidual reaction to encourage implantation and development. Decidua itself is not necessary for implantation or the continuation of a pregnancy.

The authors wish to acknowledge with grateful appreciation the many suggestions and aid given by Dr. A. T. Hertig in the preparation of this report.

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history of leucorrhea and spotting for the past three years. For the last three months she had been passing clots. She has lost 20 pounds during the past six months. She had no pain, but complained of a feeling of exhaustion.

Her past history was essentially negative. She had had two full-term children, delivered normally, and one spontaneous miscarriage at eight weeks. Meno-

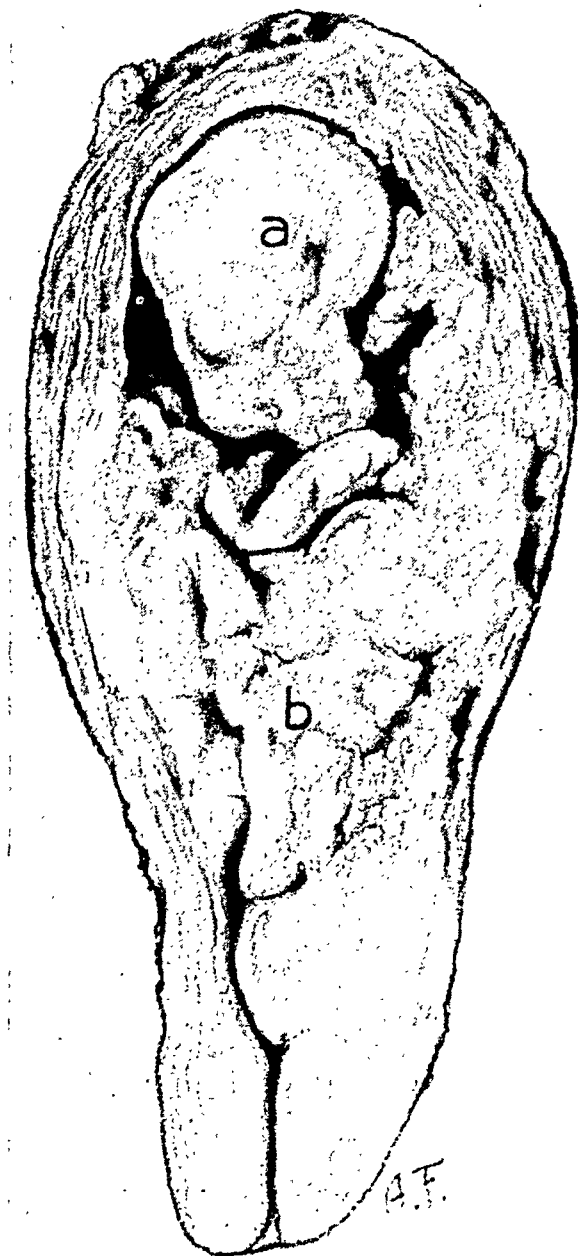


Fig. 1.—Gross specimen showing (A) sarcoma, (B) adenocarcinoma.

pause occurred at the age of 51 years. She had always been in good health until the appearance of the first of the above noted symptoms three years ago.

Physical examination showed a well-developed woman, weighing 116½ pounds. Her temperature, pulse, and respiration were normal, as were her heart and lungs. Her blood pressure was 160/92; hemoglobin, 78 per cent. Vaginal examination revealed a good parous pelvic floor. The cervix was

Microscopically, these tumor masses were large, round, and spindle-cell sarcomas with numerous giant cells. The endometrial covering was typical adenocarcinoma. The myometrium was free from sarcoma; and the adenocarcinoma of the cervix was a separate growth, independent from the carcinoma of the body of the uterus.

Saphir and Vass, in their review of the reported cases of carcinosarcoma, were not convinced that all of them were actually carcinoma and sarcoma. Of the 153 cases which they reviewed, only three or four qualified as multiple neoplastic processes. Of 36 growths occurring in the uterus, they did not believe any to be true coexisting carcinoma and sarcoma. The most common sources of error in interpretation lay in the resemblance to a sarcoma caused by a marked stromal reaction to the invasion of carcinoma, the extreme variability of epithelial cells, especially when transitional or spindle forms were present, and the part played by chronic inflammation in the production of pleomorphic cells resembling sarcoma. Therefore, these authors questioned the coexistence of carcinoma and sarcoma in the great majority of the reported cases.

Hoffman, in his studies, reported a case of myosarcoma and papillary carcinoma of the uterus and believed them to be two separate entities, that is, multiple primary malignant tumors, each having its own histologic characteristics. Since the predominant characteristic of this carcinoma was its papillary arrangement without any surrounding fibrosis, there was little reason to interpret the separate sarcoma as an extreme fibroblastic reaction to the carcinoma. Likewise, there was no inflammatory change which might serve as a cause of extreme fibroblastic reaction.

Barnes reported two cases in which two independent primary growths were demonstrated. In neither case was there definite evidence that the sarcoma had arisen on the basis of malignant fibroid degeneration. On the contrary, there was a distinct topographic separation of the two tumors in the uterus.

In a case of sarcocarcinoma of the uterus, reported by Jaffe, the author believed that the carcinoma caused the sarcomatous degeneration of the stroma. He did not think it a common stroma which reacted against the irritation by the carcinoma; the tendency for its excessive growth was already present, and the carcinoma merely enhanced this state. In the portio of the uterus there was the disposition to malignant new formation in both the epithelium and the mesenchyme. The first to become manifest was the carcinoma, which in turn caused the appearance of the sarcoma.

A case of carcinoma and sarcoma in the same uterus was described by Watson. Since both ovaries were involved, a complete hysterectomy with removal of the adnexa was performed. Examination showed a typical adenocarcinoma of the endometrium and beneath it, but completely separated from it, an area of abnormal tissue that would be classified as sarcoma because of its histologic characteristics. The ovarian mass on the right side showed typical adenocarcinoma, whereas that on the left side displayed characteristics of sarcoma rather than of carcinoma. Because of this unusual condition Watson stated that it was an open question whether his case should be called one of carcinoma and sarcoma in the same uterus or whether it should be classified as "carcinoma with a bizarre type of anaplasia."

Case Report

A case from my own experience is that of Mrs. R. B., a widow, white, 55 years old. A previous diagnostic curettage resulted in a diagnosis of adenocarcinoma of the corpus. She was admitted to the hospital on Nov. 2, 1943, with a

Follow-Up.—The patient reported for a follow-up examination six months later, at which time she stated that she felt well and had no complaints. She had gained 9½ pounds; hemoglobin was 82 per cent. Examination showed the vaginal vault to be clean and well suspended. No tenderness or thickening was noted in the pelvis. She was seen six months after that; and, although she had lost six pounds, she said that she felt well and was going to business regularly. The pelvic findings were the same as those of the previous visit. She was seen on Nov. 2, 1945. She still felt well and had no complaints. Her weight was 119 pounds; hemoglobin, 78 per cent. Urine examination gave negative results. There was no change in the pelvic findings. She stated she remained well until March 24, 1946, when she was operated upon by Dr. Robert

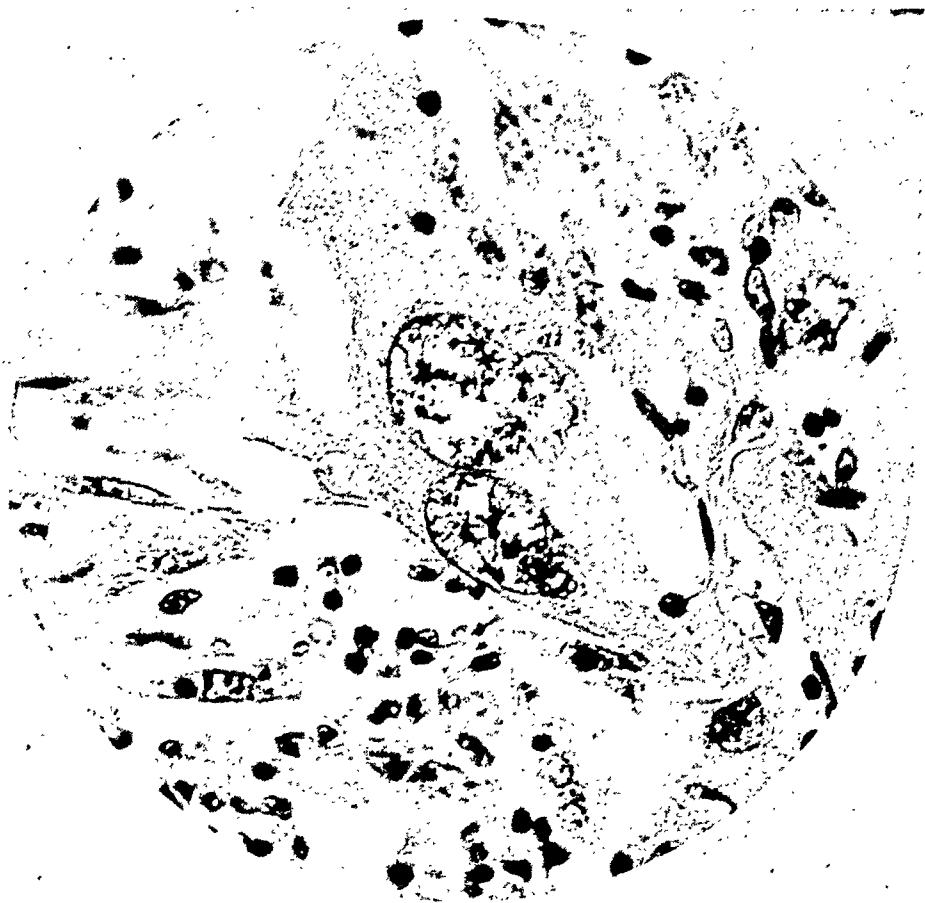


Fig. 3.—Sarcoma of uterus. Picture shows large bizarre giant cell with two nuclei of unequal size. ($\times 450$.)

Moseley of Kingston, N. Y., for strangulated right femoral hernia. The badly damaged loop of small intestine could not be delivered through the femoral ring, so a laparotomy was done. An adenocarcinoma, primary in the ilium, was found about three inches proximal to the strangulated loop. The tumor was firmly adherent to the lower abdominal scar, and there was extensive involvement of the mesenteric and retroperitoneal glands at the base of the mesentery. There was no palpable liver metastases. The hernia was repaired, and a wide resection of the ilium was done with a side-to-side anastomosis. The glands could not be removed. She received a course of radiation therapy (3,000 RU) at the Memorial Hospital. On June 28, 1946, she was symptom

clean and smooth. The uterus was slightly enlarged, regular in shape, mobile, and in fairly good position. No lesions were found in the adnexa.

Operation.—When the abdomen was opened, no adhesions were found. The uterus was somewhat enlarged, slightly globular, and symmetrical. The adnexa were atrophic. A complete hysterectomy was done, including removal of the tubes, ovaries, and a moderate cuff of vagina. Except for a moderate staphylococcus infection of the abdominal wound, her postoperative course was uneventful.

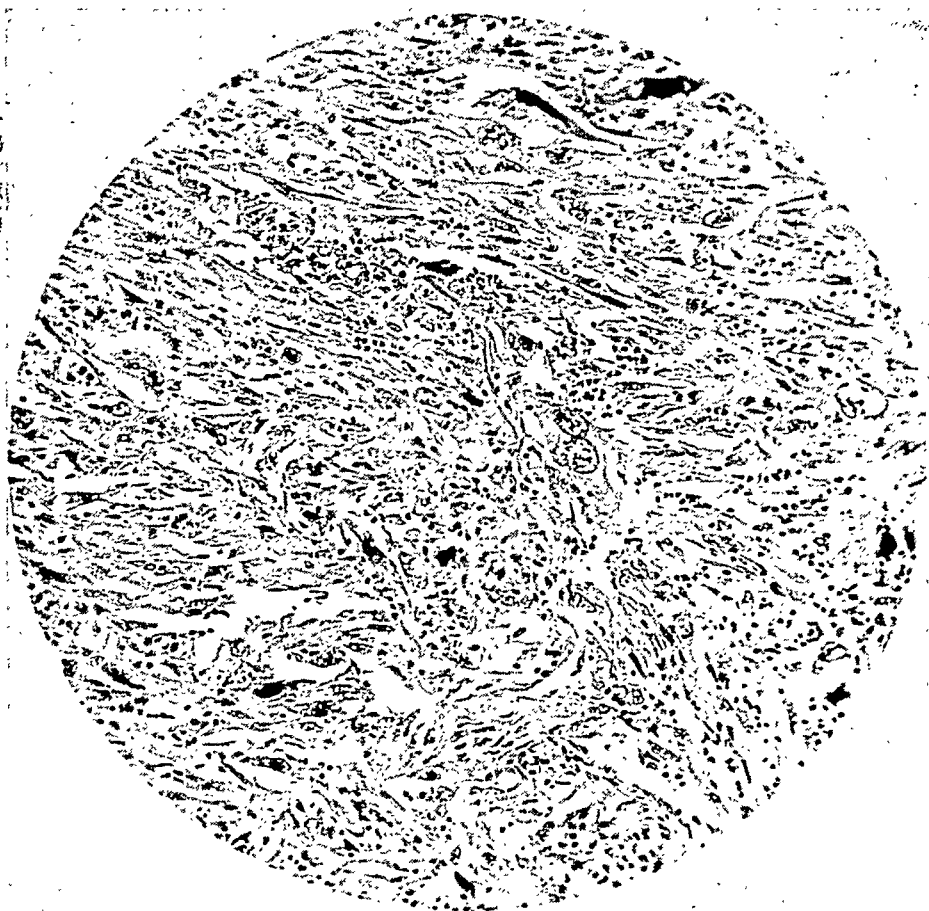


Fig. 2.—Sarcoma of uterus. Note profusion of spindle cells together with scattered giant cells. (X110.)

Pathologic Examination.—The specimen consisted of a uterus including the cervical portion with both tubes and ovaries attached. The uterus was slightly enlarged, weighing 110 Gm. and measuring 9 cm. by 4 cm. by 5 cm. When the uterus was sectioned, an irregular gray, solid, friable tumor was revealed, filling and distending the endometrial cavity and replacing the entire endometrium. The tumor penetrated the myometrium in some areas. In general, the myometrium was thin. The tubes and ovaries appeared atrophic.

Microscopic Examination.—The bulk of the tumor was a typical cylindrical cell adenocarcinoma with well-formed glands lined by tall columnar cells. Sections prepared from the fundal portion of the tumor (Fig. 1A) showed it to be sarcoma. It was composed chiefly of interlacing bundles of plump spindle cells. Many of the cells were anaplastic; few were large, bizarre, giant in size.

Diagnosis.—Adenocarcinoma and sarcoma of the uterus.

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free, had gained weight, and there was no palpable mass in the abdomen. She was last seen Dec. 13, 1946, and stated that she had no complaints and had gone into business for herself. Her weight was 118 pounds; hemoglobin, 60 per cent. Pelvic findings were the same as of previous visits.

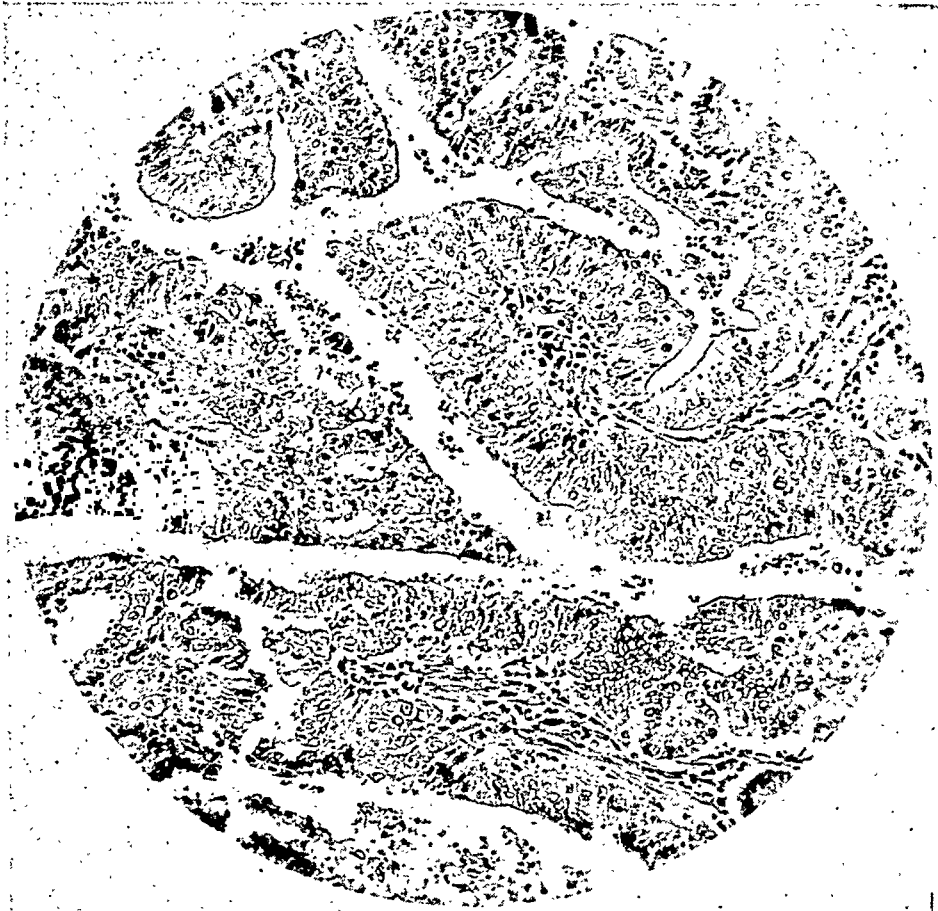


Fig. 4.—Carcinoma. Note cylindrical cell adenocarcinoma. (Hematoxylin-eosin stain, $\times 110$.)

Summary

1. The coexistence in the same uterus of two tumors, one an adenocarcinoma and the other a sarcoma, is rare, only about 28 cases having been reported.
2. A review of the literature on the existence of carcinoma and sarcoma in the same uterus revealed considerable confusion in terminology. Many tumors are composed of irregular and nondifferentiated cells, which make the origin difficult to determine. This difficulty has led to much confusion in the nomenclature and to the introduction of a great many unnecessary names. As new light is thrown on their origin, there is no doubt that many pathologic conditions now considered sarcoma will be classified as separate types of malignancy.
3. A case of coexistent adenocarcinoma and sarcoma of the uterus is presented in the hope that it may be of some little help in the subsequent classification of these tumors.

the cervical canal about 9 o'clock, there was an area which was a rather flannel red and which bled when suction was exerted on it to secure a spread. The cervix was firm but not hard, felt somewhat irregular. The uterus was small, in good position, easily movable; the fornices were negative. Movement of the cervix was slightly painful as was pressure on the uterosacral ligaments, but there was no limitation of movement of the cervix. Perineum was well healed, no cystocele, no rectocele.

Spreads of the secretion from the vagina and cervical canal were made and these were stained by a modification of the Papanicolaou stain. In addition to many leucocytes and blood, cells consistent with a diagnosis of epidermoid carcinoma were found. This finding was confirmed by two other laboratories. Repeated smears were made of cervical and vaginal secretions and all showed irregularly shaped cervical cells with marked heteroplasia (Fig. 1). On January 5, a wedge-shaped piece corresponding to the reddened portion of the cervical canal was removed for microscopic study. Sections from this material varied from practically normal with a small amount of round cell infiltration to definite Grade II squamous cell carcinoma of the cervix with invasion of the cervical mucosa, some areas exhibiting attempts at pearl formation.

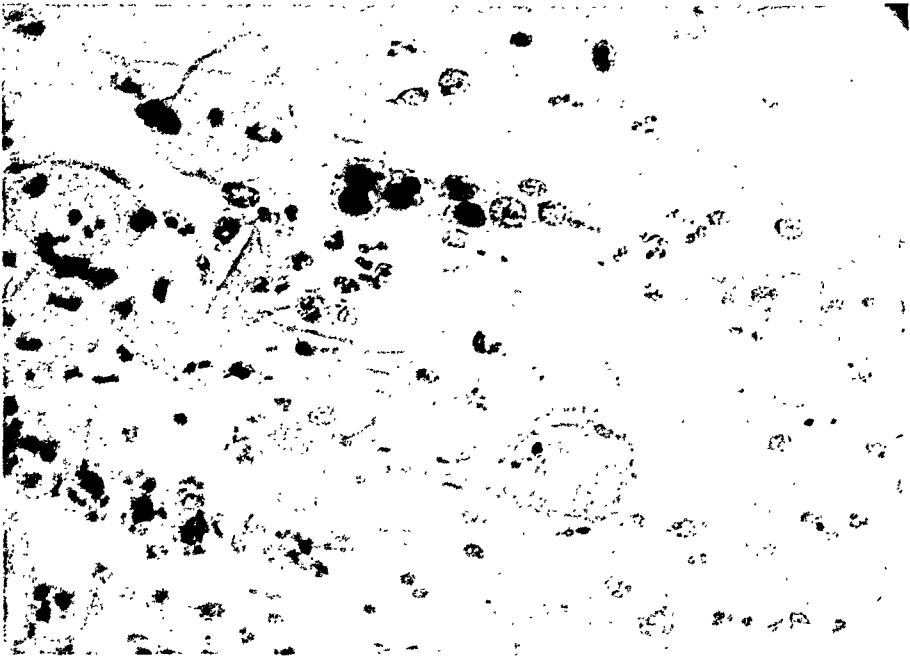


Fig. 1.—Stained vaginal spread. Note malignant cells in upper center.

On Jan. 28, 1946, the uterus, tubes, and ovaries were removed with a $\frac{3}{4}$ inch cuff of vagina by abdominal operation.

Macroscopic examination revealed an ulcer 1 cm. from the external os measuring 2 cm. by 1 cm. On section there was a growth in the cervix 1 cm. in depth, definitely confined to the cervical canal and, while it extended down into, it did not penetrate through the cervical tissue, there being 5 mm. of apparently uninvaded tissue external to it.

Sections from the cervix revealed infiltration of an epithelial malignant tumor. The tumor was growing in the form of broad flat bands and long fingerlike processes with occasional groups of isolated cells. These cells were quite large with variations in shape and with large, sharply defined hyper-

CARCINOMA OF THE CERVIX PRIMARILY DIAGNOSED BY THE STAINED VAGINAL SPREAD*

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FROM the gynecologist's viewpoint, the early diagnosis of carcinoma of the reproductive organs is the principal objective of the physical examination of women at stated intervals, annual or semiannual. As long as the physician had to rely on historical, tactile, and visual sources for evidence of neoplastic change, he was constantly aware of the limitations inherent in diagnosis and prognosis, based on these procedures. With the advent of stained spreads of vaginal secretions, a study of their cytology opened up whole new fields. Through these studies he becomes familiar with endocrine changes and activities and variations in therapeutic responses within reasonably definite limits. In suspected cancer cases, the value of these studies has been too frequently attested to need repetition.

Advantages that these spreads present are that they may be made as frequently as the curiosity of the examiner dictates, are inexpensive to carry out, and present no inconvenience or danger to the patient. That these spreads have the weight of a biopsy is not suggested. However, when the cytologist finds cells of suspicious appearance he is then induced to make further studies and to keep the patient under careful observation at frequent intervals. With recurrence of malignant appearing cells, a biopsy then is indicated. In addition, he must follow his biopsy into the pathologic department and insist on sectioning of the entire block. The importance of this is emphasized below.

Carcinoma of the cervix and fundus in the early or preinvasive stages presents the greatest challenge for prompt recognition and, at the same time, offers the greatest chance for complete cure with the least surgical risk. With these considerations in mind, we have for the past two years practiced the study of stained cytologic spreads as just as regular a part of the examination of the patient as examinations of the blood, urine, and other routine laboratory procedures. The extraordinary value such studies may have is illustrated by the following case report.

This married, white patient, aged 38 years, reported for annual physical checkup on Dec. 12, 1945. Her periods had been perfectly regular until November 5, when her menstrual flow began on the expected date and lasted as usual for four days. Following this, there was a discharge of mucus occasionally tinged with blood and associated with some backache. The bleeding was increased by housework and occurred once or twice following coitus. The discharge had never been sufficient to require wearing a pad. There were no associated symptoms except for an increased frequency of urination for a few days from November 29. There had been one pregnancy, eighteen years before, with a rather difficult delivery, and the cervix and perineum were repaired in 1936.

The physical examination was entirely negative, with a hemoglobin of 90 per cent and a weight of 120 pounds (as usual). The abdomen was relaxed and no tenderness or masses were palpable. Cervix was rather pale, somewhat irregular, resembling a cervix that had had a plastic repair. Just within

*Presented at the annual meeting of the South Atlantic Association of Obstetricians and Gynecologists, Greensboro, North Carolina, February 15 to 16, 1946.

While the history given by this patient is perfectly consistent with that associated with early neoplastic change, and in the light of subsequent findings, one is impressed with the story of bleeding associated with trauma, such a history is daily recorded in women of the fourth decade in the absence of malignancy. This reassuring fact, taken with the reluctance of the clinician to do a biopsy or a diagnostic curettage, often accounts for the average delay of nearly seven months between the first visit of the patient and her receiving definitive treatment. It has been estimated that delay in the presence of carcinoma decreases the chance of cure by 3 to 4 per cent per week. In this individual cells were found which two independent observers confirmed as consistent with undoubted squamous cell carcinoma. These findings certainly impelled a biopsy which, without their discovery, might easily have been delayed to the serious depreciation of the hope of operative cure. As in the case reported by Ayre, the first cuttings were entirely negative for cancer and exhibited only inflammatory changes. A less zealous laboratory, and without the cytologic findings, might have failed to make the further sections which revealed carcinomatous findings.

False positive diagnoses of carcinoma from vaginal spreads will probably be made by the unwary and have been reported by those who may be considered experts. An error of 2.9 per cent in "negative called positive" occurred in a series of 861 cases reported by Meigs. A conservative attitude must be maintained when such findings are the sole basis for the diagnosis of uterine carcinoma. However, Papanicolaou and others have reported such cases in which positive cells were found with no clinical supportive evidence which, within six months, have been confirmed by curettage or biopsy.

False negative reports are the peril of the uninitiated and may represent insufficient study by the most adept. Thus Meigs shows an error of 10.3 per cent in 1,015 cases, of which 154 were shown to have cancer on microscopic section. Sixteen spreads of these proved patients were negative: 7 of the 16, on review of the slides, showed cancer cells and were missed because every field was not examined. There is thus a corrected error of 5.7 in false negatives in this report.

From these studies we may assume an expectation of 95 per cent correct in both positive and negative reports—an error which may be expected to diminish with further experience.

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chromatic nuclei, with occasional mitoses (Figs. 2 and 3). (The microphotographs do not show with sufficient clarity what is dramatically apparent in the microscope—the absolutely identical appearance of the cells in the spreads with those seen in the tissue sections.)

Microscopic Diagnosis.—Squamous epithelioma of the cervix, grade II.

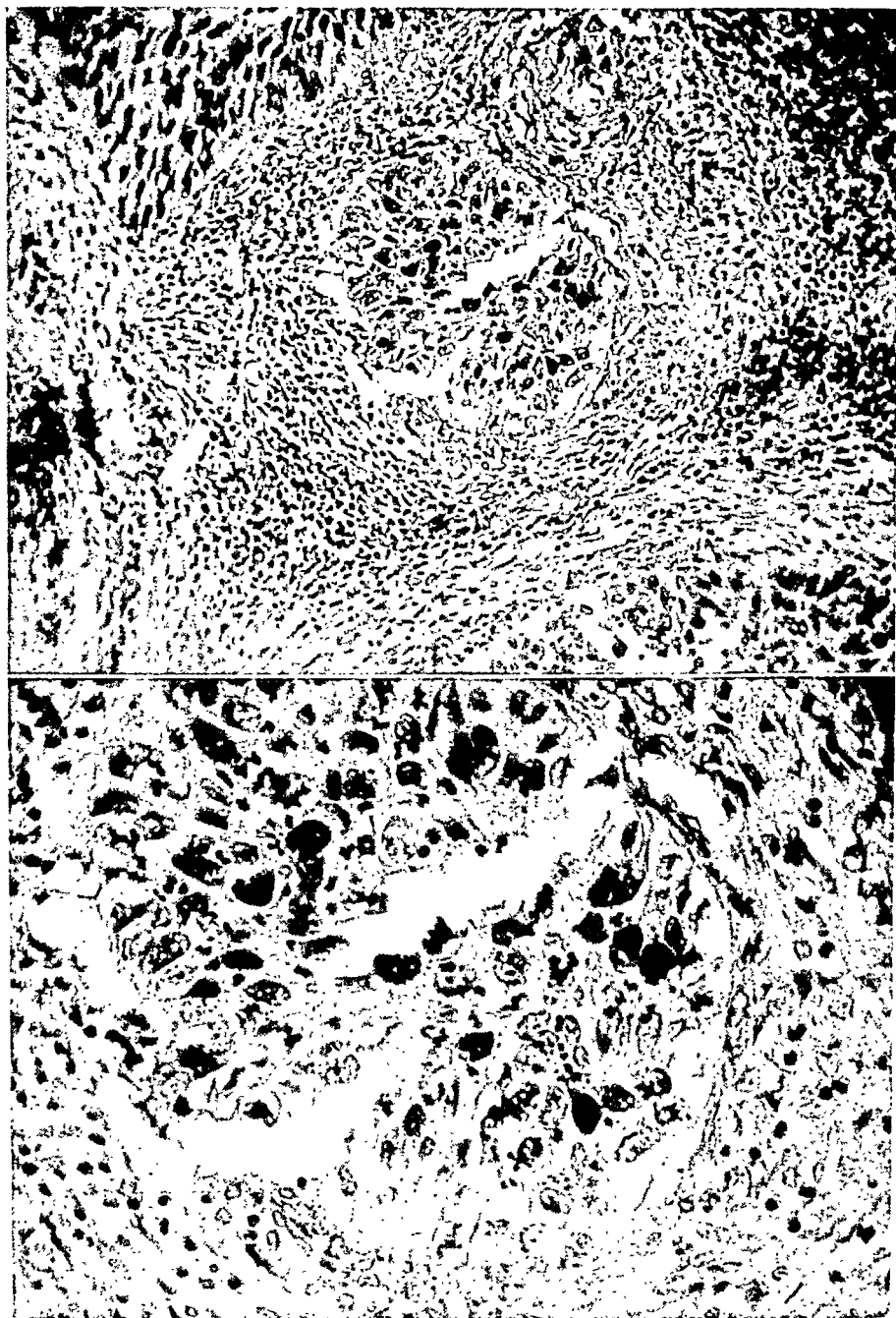


Fig. 2.—Photomicrograph (low power) operative specimen.

Fig. 3.—Photomicrograph (high power). Note resemblance of cells to those in Fig. 1.

Comment

It is to be emphasized that this patient did not come in because of the reddish discharge, as this history was obtained only on careful questioning. She had been in the habit of a "November examination" for five years, and it had been delayed by changing her residence to this city.

thorax was normal except for flaring of the left costal margin. The umbilical cord had been tied and cut recently. The anus was patent. The genitals appeared normal for a male infant. Both testes were palpable in the inguinal canal. The lower extremities were grossly normal except for the feet. There was a lateral displacement of both feet on the lower end of the tibiae and fibulae, giving the feet a varus deformity. The feet were broad and flat. The lateral three digits of both feet were webbed and curved medially. The medial digit of each foot was short and curved laterally, while the second digits were long and straight. The lungs weighed 30 grams. The right lung was grossly normal. The left lung was a deeper bluish red. Cut section was not remarkable. Both lungs floated. The adrenals together weighed 8 grams. They were normal in size, shape, and consistency, and on cut section. The kidneys were grossly abnormal. The right kidney was 3.5 cm. in length, weighed 20 Gm. and felt cystic. On cut surface the calyces were large cystic structures obliterating all but a thin margin of cortex. The left kidney was 2.0 cm. in length and weighed only 10 grams. The surface was studded with small subcapsular, thin-walled cysts which were distended with urine. On cut surface more dilated calyces were apparent. The ureters were very tortuous, dilated, and thickened, but no obstruction could be demonstrated. The bladder was normal in size, shape, and position. There was marked congestion of the mucosa of the bladder.

Microscopic examination revealed the lungs to be congested and atelectatic, but there was no marked hypoplasia. The kidneys were made up of large calyces lined with transitional epithelium, which in some areas extended to within a few millimeters of the renal capsule. The glomeruli show diffuse hyaline degeneration in varying stages similar to a picture of subacute glomerulonephritis. There was interstitial fibrosis with tubular atrophy. One area of the bladder showed marked submucosal hemorrhage.

In summary, our case seemed to be one of congenital hydronephrosis, diffuse hyaline change in the glomeruli, and bilateral tortuous ureters. Secondary to the hydronephrosis and glomerular degeneration there was interstitial fibrosis, tubular atrophy, resulting in a diminution of normal kidney tissue. The lungs were atelectatic and showed only a slight tendency to hypoplasia. There were multiple deformities of the osteocartilaginous structures.

Our case would indicate that intact renal physiology is necessary to the normal development of osteocartilaginous structures. Renal agenesis is merely one form of renal insufficiency in utero, and this case demonstrates a second.

CONGENITAL HYDRONEPHROSIS

LIEUTENANT MICHAEL L. ALLEGRETTI, MEDICAL CORPS, UNITED STATES NAVY

(From the U. S. Naval Hospital, U. S. Training Center, Great Lakes, Ill.)

RECENTLY Potter reorted 20 cases of congenital renal agenesis all of which were remarkable because of the presence of a peculiar facial appearance and hypoplasia of the lungs. One hundred forty cases have been previously reported. In addition to the peculiar facial appearance and hypoplasia of the lungs, all of the cases showed skeletal anomalies. These anomalies were most apparent in the lower extremities. All of the cases showed a complete absence of renal tissue, including the absence of both ureters.

Our case of congenital hydronephrosis is interesting, because it simulates the cases mentioned above in every respect except for the fact that both kidneys were present. However, there was considerable atrophy of renal parenchyma due to a bilateral congenital hydronephrosis. We feel that this resulting renal insufficiency is enough to bring about the changes mentioned above, and that a complete renal agenesis need not be present.

The infant's mother was a 23-year-old, white, para i, gravida ii. Her first pregnancy had terminated spontaneously at eight months. A 7-pound male was delivered who had a cleft palate, and lived only eight hours. No post-mortem examination was made. Three weeks before her expected date of confinement with her second pregnancy, the mother entered the hospital because of vaginal bleeding. Her pregnancy had been normal for eight months with no signs of pre-eclampsia, acute exanthem, or fetal abnormality. Admission examination revealed a soft cervix dilated 1 cm., and moderate bleeding from the cervical os. The blood pressure was 104/64. The fetal heart was easily heard to be regular at a normal rate. The labor lasted twelve hours, and the mother received $\frac{1}{150}$ grain of scopolamine followed by N₂O and ether inhalation anesthetic during the second and third stages. The baby was resuscitated with moderate difficulty. Shortly after birth, he became cyanotic intermittently and survived only seven and one-half hours. The maternal and paternal family histories were noncontributory. The mother was Kahn negative and Rh positive. At necropsy the pertinent findings were as follows:

The body for examination was that of a small male infant having a crown rump measurement of 28 cm. Several gross abnormalities were obvious. The head was normal in size, but the sagittal suture was separated 0.5 cm. throughout its length. There was a moderate amount of fine black hair on the head. The ears arose from the head at points lower than the level of the eyes, approximately opposite the level of the mouth. The bridge of the nose was convex in its sagittal plane with no concavity at its upper end, and sharp and flat at the tip. The tongue was bifid and short. From the right facial area a 0.75 cm. tongue of lymphoid-like tissue protruded into the oral cavity. There was a small cleft in the palate involving mainly the uvula about 0.5 cm. in length. The line of fusion of the palate was accentuated and extended as a furrow through the alveolar ridge. The mandible was 1.5 to 2 cm. shortened from the angle to the mentum so that the chin was markedly receding. The upper extremities were grossly normal except for the hands. The thumbs were short, curved medially under the second digits which were long, and straight. The lateral three digits of both hands curved medially under the second digit. The

trophic cervix during a long labor, it is stimulating to learn that Marmaduke Burr Wright insisted, in 1876, that "no man is justified in using forceps with an undilated os." Apparently his teaching at the time was a minority protest against current practice. The handling of incomplete abortion was as moot a question then as it is today; Stevens led one faction of doctors with the motto of "Time, Rest, and Laudanum," while Zinke captained the other with the statement: "No woman is safe till the uterus is empty." Throughout the years the papers presented at the society meetings, critically discussed, have been the basis for some important contributions to the professional literature of the country. The seventieth anniversary celebration of the founding of the Cincinnati Obstetrical Society is a milestone in the steady progress that has been made in the practice of obstetrics and gynecology, and is a token of enthusiasm for continued effort.

Special Article

THE CINCINNATI OBSTETRICAL SOCIETY, SEVENTIETH ANNIVERSARY; AN HISTORICAL NOTE

ARTHUR G. KING, M.D., CINCINNATI, OHIO

SEVENTY years ago the most recent advance in the field of obstetrics and gynecology was Emmett's trachelorrhaphy and the surgical repair of the perineum. The hydrostatic bag was unknown and Dührssen was yet to propose his incision of the cervix. The first uterine suspension had not yet been done, and the streptococcus was unknown. The Porro technique of hysterectomy had just been announced as a lifesaving measure in cesarean section, and it was to be five years before Saenger proved the value of suturing the uterus during the operation. Only 108 cesarean sections had been done in the United States, and the mortality was 59 per cent. Although a successful abdominal delivery had been performed in 1827 in neighboring Newtown, Ohio, it was to be two years before the first cesarean section was done in Cincinnati.

Refulgent in the inspiration and tradition of Dr. Daniel Drake, Cincinnati, a city of 230,000, had about 600 doctors in practice. There were three medical schools: The Medical College of Ohio, The Miami Medical College, and the College of Medicine and Surgery. Three medical journals were published regularly: *The Lancet-Observer*, *The Clinic*, and *The Cincinnati Medical Journal*. And there were two general medical organizations: The Academy of Medicine, and a dissident group called The Cincinnati Medical Society, a name used as far back as 1819.

The first organization in the United States devoted to obstetrics and gynecology was the Obstetrical Society of Boston, formed in 1861. In 1864 the New York Obstetrical Society was started, and in 1868, the Obstetrical Society of Philadelphia. The fourth city in the United States to have a group of doctors meeting for "the promotion of knowledge in all that pertains to Obstetrics and Diseases peculiar to Women" was Cincinnati. In 1876, Thaddeus A. Reamy formed the Cincinnati Obstetrical Society, and it has been in active continuous existence ever since. Starting with eleven members, a total of one hundred thirty names are on the roster, including Reamy and J. W. Underhill, who were among the first men elected to the American Gynecological Society, founded the same year, Giles S. Mitchell, one of the founders of the American Association of Obstetricians and Gynecologists, and E. B. Stevens, editor of the *Cincinnati Obstetrical Gazette*.

For a number of years after the founding of the society, the complete transactions were published in the *American Journal of Obstetrics and Diseases of Women and Children* started only eight before. Many of the early papers represented great advances in gynecologic thinking and described procedures which for the time were very radical. The early minutes reveal vigorous discussion and trenchant criticism, and often the extemporaneous remarks were longer and better documented than the essays. Although it is amusing to read of a serious advocacy of the use of leeches to reduce congestion in a hyper-

In addition, forty-two medical schools actively present material on medical genetics in connection with didactic or clinical courses.

This progress is highly commendable, but much remains to be done. Every premedical student should be required to take a course in the principles of genetics, and every medical student should have training in medical genetics and its practical applications. Only then will the remarkable strides in this medically important science be made functional and profitable. To those engaged in obstetric practice, these facts are of particular import.

An International Congress of Obstetrics and Gynecology

IT WOULD appear appropriate to continue the holding of international congresses in this important field of medicine at definite intervals. The year 1947 marked the Bicentenary of the Rotunda Hospital which afforded an opportunity, while commemorating the founding of a great and well-known institution, to develop a gathering of obstetricians and gynecologists from many parts of the world. The program of this meeting held during the past July disclosed a representation from 14 different countries and was largely devoted to obstetric topics including the history of midwifery, puerperal sepsis, eclampsia, shock in obstetrics, sterility, fetal and neonatal mortality.

The desirability of bringing together the workers and practitioners in the domain of this branch of medicine is one of paramount importance, for an exchange of ideas is a contributing factor to progress. The great war has disrupted such gatherings but the advent of peace, even if this is not attained as rapidly as one might wish and hope for, nevertheless should bring about a resumption of relations between professional men of the world as soon as possible. Thought, therefore, may be given to the possibility of holding another congress in the near future, say in 1950, and preferably in the United States, where none has ever been held. We would suggest a city in the Eastern seaboard, large and readily accessible, such as New York, with its extensive hospital facilities, an abundance of hotel accommodations and many other attractions. The active promoting agency for the purpose might well be the American Committee on Maternal Welfare which has developed a machinery for such purposes, as evidenced by the two previously held national congresses. It would seem desirable that steps be taken at an early date to organize the project so that invitations might go forth to participate in the program by countries, institutions, and individuals, and the necessary support developed by our various organizations devoted to the specialty. The United States, because of its many advances in medicine, and its well-developed interest in obstetrics and gynecology, would be the logical host to develop an international gathering of this nature.

Editorials

The Need of a Knowledge of Medical Genetics

THE recent observance of the 100th anniversary of the New York Academy of Medicine highlighted anew a problem which has been too long neglected, but which is growing rapidly in importance and cannot be stressed too strongly. The need for a thorough training of medical students in the principles and practical applications of medical genetics is becoming more apparent with each new discovery in the field.

At this gathering Dr. H. J. Muller, who received the Nobel Prize in Medicine for 1946, discussed the question of the accumulation of mutations in human populations, both from natural causes and from artificial radiation, including x-rays and the emanations from nuclear fission such as those used in the atomic bomb. He presented valuable suggestions for "mutational prophylaxis."

Dr. Laurence H. Snyder of the Ohio State University, in 1940, in the Biggs Lecture on Medical Genetics and Public Health, then discussed the training of physicians in this field. He pointed out that the adequate understanding of Dr. Muller's important presentation, which has a bearing on the lives of all of us, is dependent upon a knowledge of the basic principles of heredity. Furthermore, the physician needs not only a basic acquaintance with genetics, but a specialized knowledge of medical genetics, because of the very practical benefits which this may bring to the practice of medicine.

Dr. Madge T. Macklin has for years stressed at every opportunity the need for medical genetics in the medical curriculum. At first only a voice crying out in the wilderness, she has been joined by a veritable chorus. The researches of Landsteiner, Levine, Wiener, Snyder, Wilson, Schweitzer, Neel, Allan, Cotterman, Penrose, Haldane, and a host of others have unearthed material of great importance to the physician, but requiring a knowledge of medical genetics to be adequately understood. The applications of these researches in diagnosis, in preventive medicine, in genetic prognosis, and in forensic medicine are too important to be neglected any longer.

Medical schools are slowly but surely responding to this challenge. Fifteen years ago Macklin conducted a survey which revealed the fact that not a single medical school at that time offered a course in medical genetics, and only two schools presented any material on the subject in other courses. Snyder has also presented the results of a similar survey just completed. Today three medical schools have required courses in medical genetics, four have elective courses, and ten more are planning to present such courses in the near future.

electrocardiography to several states of pregnancy. These investigators attached a twenty-power amplifying tube in front of a small model Siemens electrocardiograph. They obtained their best results using abdominal applications, one electrode being applied above the symphysis and another on either side of the fundus. In the cases of early pregnancy (third and fourth month of pregnancy) only two electrodes were used, the one a lead disc on the end of an insulated rod placed against the portio, and the other immediately above the symphysis pubes. After a long period of studying more trustworthy methods, 30 cases of pregnancy, in different stages, were submitted to electrocardiography; viz.: five cases during the tenth month, 11 cases in the ninth, four in the eighth, three in the seventh, two in the sixth, three in the fifth, two in the fourth, and one in the third month. Positive results were obtained in 29 cases, and negative in the thirtieth case pregnant five months. An induction of labor produced a dead and macerated fetus.

The writers conclude: (1) with the aid of an electrocardiogram it is possible to determine quickly whether the fetus is alive or dead, (2) the electrocardiogram is useful in early pregnancy diagnosis, (3) the fetal heart rate could be proved independent of the maternal heart rate, (4) the electrocardiogram was of no value in determination of the presentation, position or attitude of the fetus, and (5) the fetal heart action disorders, excluding arrhythmias could not be diagnosed by this method. The article is well illustrated with electrocardiographic reproductions.

C. E. FOLSONE.

Vilter, Carl F., Morgan, Dorcas, and Spies, Tom D.: *Nutrition in Pregnancy. The Effects of Dietary Deficiency in Pregnancy and the Detection and Treatment of Nutritional Deficiency Diseases*, Surg., Gynec. & Obst. 83: 561, 1946.

This paper presents a short but concise review of some of the current literature on nutrition in pregnancy. The study herein briefly discussed is one in which 229 mothers between the ages of 18 and 45 years who were patients at the Nutrition Clinic in Birmingham, Alabama, were considered in relation to deficiency diseases. Only 4 of the 229 mothers had definite symptoms of nutritional disease prior to the first pregnancy. However, 135 developed symptoms during lactation or pregnancy, and the symptoms appeared to be more frequent during the last trimester. Methods of prevention of nutritional deficiencies are presented, and means of diagnosis are described. The authors state that the principles of treatment for nutritional disease occurring in pregnancy do not differ from those in the nonpregnant woman. A high caloric, high protein diet with adequate vitamins and minerals is recommended by the authors.

L. M. HELLMAN.

Misrahy, Georges A.: *The Metabolism of Histamine and Adenylic Compounds in the Embryo*, Am. J. Physiol. 147: 462-470, 1946.

Misrahy, University of Cairo, Egypt, using two separate batches of about 200 eggs each, traced the development of histamine and adenosine, two of the most powerful vasodilator substances among the body "metabolites," throughout the hatching period. It was ascertained as a preliminary to this study that nonfertilized eggs were completely free of these substances.

The author was able to demonstrate that the production of these two substances ran approximately parallel to the growth of the embryo, save that the peak increase of histamine was delayed by two to three days as compared to adenosine. He discusses and compares organ distribution of these two active agents in the embryo and the adult. The metabolism of histamine and adenosine was similar in the chick and rat embryos, and considers these two substances are the result of metabolic processes in the embryo itself and are not supplied through the placenta in a ready-made form.

These observations in this basic study, well documented with two figures and four tables, will be of much interest to obstetricians interested in the relationship of these compounds to human pregnancy and some of its obstetric accidents.

C. E. FOLSONE.

Department of Reviews and Abstracts

Selected Abstracts

Pregnancy, Physiology, Etc.

Harjola, Oiva: Contribution on the Knowledge of the Peripheral Blood Picture During Pregnancy and the So-Called Anemias of Pregnancy, *Acta obst. et gynec. Scandinav.* 26: 1-130, Supplement 3, 1946.

Harjola, of Helsinki, considers in great detail the peripheral blood pictures among 220 women subjects divided into the following four groups, 16 nonpregnant normal women; 82 normal and pregnant women; 71 pregnant cases exhibiting an anemia, as determined by Sahli hemoglobin values between 60 to 69 per cent; and, 51 cases of pregnant subjects, each having a Sahli hemoglobin less than 60 per cent.

The author finds that the color indices of the pregnant normal woman compare favorably with those of the normal nonpregnant women, save in certain factors of difference which occur in the former during the latter part of their antepartum period. At this time the reticulocytes increase 35 per cent; leucocytosis occurs late; the neutrophilic leucocytes show a shift to the left (younger forms in the smear), and the serum iron values are increased. Pregnancy does not influence the diameter of the erythrocytes or cause anisocytosis. The cell volumes and saturations are likewise not affected by pregnancy.

In the group of milder anemias in pregnancy the writer observes these more significant conclusions—when the hemoglobin decreases, the red cell count decreases at the same time, but the color index remains constant; as the new red cells develop, the reticulocytes increase to an average of 13 per cent; the drop in hemoglobin value causes no effect upon the mean cellular diameter of the erythrocytes, but the anisocytosis increases by 14 per cent. As the hemoglobin decreases, a hyposideremia develops in about one-third of the cases which evidenced a decrease in serum iron.

In the group of more serious anemias of pregnancy, among that series having a Sahli hemoglobin value less than 60 per cent, the writer concludes with these more significant findings—as the hemoglobin falls the number of erythrocytes and their color indices markedly drop in all cases; reticulocyte response show increases in more than 50 per cent of the cases; there is a gradual increase in the neutrophilic leucocyte count, and a shift to the left with each successive month of pregnancy; anisocytosis increases on an average of 18 per cent, and the mean of the serum iron value drops to 51 per cent, as compared to those pregnant and in good health. The author concludes that gastric acidity exerts no decisive influence upon the development of anemias even among those cases exhibiting the more serious states during their pregnancies.

The monographic article is excellently documented with many tables, figures and detailed collateral minor conclusions. C. E. FOLSOME.

Vara, Paavo, and Halminen, Eero: On Fetal Electrocardiography, *Acta obst. et gynec. Scandinav.* 26: 249-262, 1946.

The authors, reporting from the Second Women's Clinic and First Medical Clinic of Helsinki University, proposed six questions they hoped to answer anent the application of

observations, and the physician should be prepared to combat acute signs of tetany and deliver the patient in the hospital. The author does not discuss therapy, his objective being principally to suggest that there is no cause for alarm or radical treatment when this condition is found in pregnancy.

C. E. FOLSOME.

Radiation

Ritala, A. M.: Clinical Investigations of the Complication of Rectovaginal Fistula Following Radium Therapy of Cervical Carcinoma, *Acta obst. et gynec. Scandinav.* 26: 193-224, 1946.

Ritala, impressed by observation of a rectovaginal fistula developing as a complication following radium and x-ray therapy for cervical cancer that had "two fingers" of thickening in the left parametrium, decided to evaluate the cancer of the cervix cases, grades I and II, which had received radiation therapy. Excluding the surgical cases; and those without adequate follow-up, the writer considered 160 comparable grades I and II cervix carcinoma, all of which had received "Stockhold method" of radiation therapy. Follow-up and correspondence with 90 of these patients exhibited no rectal symptoms; but 70 patients, 42 per cent, suffered more or less severe rectal symptoms after radium therapy—seven cases having rectovaginal fistula and one case rectovaginal and vesicovaginal fistula.

The rectovaginal fistulas occurred six to thirteen months, on the average eleven months, after radium treatment. The average weight loss was 10 kilograms. In the eight cases of rectal perforation, the average radium dosage used was 5,600 mg. hr. in the vagina and 3,300 mg. hr. in the uterus—*exceeding* by 2,000 mg. hr. the Stockholm Method—and on an average 1,100 mg. hr. excess in the vaginal dose. Ritala stresses that the method of application of radium in this series was wrong because the lead screens, though loose and thin, were not used at all in these specific cases, as was the custom in usual cases. He stresses this point by stating—"proper training of the physician in gynecological radiation therapy as well as the use of the surgical knife is a requisite."

The writer seems little concerned about the associated roentgen therapy; cases 1 and 2 received totals of 2,000 r; cases 4, 5, and 8, a total each of 6,000 to 7,000 r; case 6, the dose in Helsingfors Contard technique; and case 7 an exceptionally large dose of 18,000 r, of which 9,000 r was given after the fistula appeared.

The author concludes by stressing the role of the traumatic cumulative effect of overdosage of radium in producing rectovaginal fistula in grades I and II cancer of cervix. He outlines in considerable detail the value of proper physician training in the management of radium therapy, and individualization of the case reporting for treatment of what are termed "early carcinoma" grade I or II.

C. E. FOLSOME.

Sterility, Fertility, Contraceptives, Etc.

Leonard, Samuel L., Perlman, Preston L., and Kurzrock, Raphael: A Turbidometric Method for Determining Hyaluronidase in Semen and Tissue Extracts, *Endocrinology* 39: 261-269, 1946.

The authors adopted the turbidometric method of Kass and Seastone for determining hyaluronidase for assaying the enzyme in semen and tissue. They report the activity in *turbidity-reducing units*.

Differences in properties of bull and human semen necessitated some modifications in preparation of the material for assay. Assays of single samples from human semen are reported. These results indicated a wide variation in the relationship between the sperm count and the enzyme concentration.

C. E. FOLSOME.

Pregnancy, Complications, Etc.

Clerc, J. P.: *A Consideration on Manual Removal of the Placenta and Its Puerperal Morbidity*, *Gynaecologia* 121: 213-220, 1946.

Clerc, of the Obstetric Clinic of Geneva, describes the results following manual removal of the placenta in 100 cases representing 1.4 per cent of the total 6,973 deliveries at that institution, from 1940 to 1944.

The author used the technique described by Killian and Schanta, and also by Knaus. After disinfection with antiseptics, the gloved hand is introduced into the uterine cavity and brought along the line of cleavage of the placenta and the uterine wall. The placenta is separated gradually and permitted to slide down the forearm. The intrauterine hand is kept in the uterus until contractions decrease its size. Every effort is made to avoid reintroduction of the hand. The manual removal is followed by a hot intrauterine irrigation, 50° C., with or without the preliminary injection of Basergine (an ergot preparation). When the return flow is clear tincture of iodine is added to the irrigant; later the iodized water is replaced by a two per cent solution of Desogene. The patient is given then a prophylactic dosage of sulfonamides (Uliron, Dagenan, or Cibazol).

The writer states that manual removal of the placenta should be performed only as a last resort; that "Basergin" should be given intravenously before the operation and strict asepsis observed.

Clerc found their morbidity low; 75 of the cases did not develop fever, while in 11 cases fever of low degree occurred sometimes following transfusions. In 12 cases complications such as thrombophlebitis, pulmonary embolism, abscesses and puerperal fever were seen. The two fatalities were ascribed to other causes—severe toxemia and syphilis in one patient, and the second patient died following embryotomy after a neglected shoulder presentation discovered eight days after rupture of the membranes of acute peritonitis.

The lapsed time between rupture of the membranes and manual removal of the placenta was 0 to 10 hours in ten of the febrile and 57 of the afebrile and 14 of the afebrile; twenty-five to forty-eight hours in three cases in each the febrile and afebrile groups; forty-nine to seventy-two hours in one febrile case and more than seventy-two hours in three of the febrile and one of the afebrile cases. In other words, 72 per cent of the 25 febrile cases had placental removal twenty-four hours or less since the rupture of the bag of waters, as compared to 95.25 per cent of the afebrile series in the same period of time. C. E. FOLSOME.

Aycock, W. Lloyd: *Acute Poliomyelitis in Pregnancy. Its Occurrence According to the Month of Pregnancy and Sex of Fetus*, *New England J. Med.* 235: 160, 1946.

The author reports 236 cases in which the month of pregnancy in which the disease occurred is known, and nine cases in which it occurred from two to twenty-three days after delivery.

Available statistics suggest that pregnancy predisposes to acute poliomyelitis, and that there is a tendency for the disease to occur in the first trimester in women who are carrying a male fetus, and in the third trimester in those who are carrying a female fetus.

JAMES P. MARR.

Redell, Gunnar: *Parathyroprival Tetany and Pregnancy*, *Acta obst. et gynec. Scandinav.* 26: 1-10, 1946.

Redell, of Falun, from his own personal observation and three others collected from Gothenburg, Stockholm, and Norrkopings, stresses the importance of serum calcium determination in women becoming pregnant who have given previous histories of postoperative tetany. The author emphasizes that Borchers's pessimistic attitude and management of parathyroprival tetany in pregnancy, and often quoted in the scanty literature, is too radical. He concludes that these cases should have better diagnostic care, more frequent antepartum

Items

American Board of Obstetrics and Gynecology, Inc.

The annual meeting of the Board was held in Pittsburgh, Pennsylvania, from June 1 to June 7, 1947, at which time two hundred fifty candidates were certified.

A number of changes in Board regulations and requirements were put into effect. Among these is the new ruling that the Board does not subscribe to any hospital or medical school rule that certification is to be required for medical appointments in ranks lower than Chief or Senior Staff of hospitals, or Associate Professorship in Schools of Medicine, for the obvious reason that such appointments constitute desirable specialist training. At this meeting the Board also ruled that credit for graduate courses in the basic sciences which involve laboratory and didactic teaching rather than clinical experience or opportunities will be given credit for the time spent up to a maximum period of not more than six months, regardless of the duration of the course.

The next written examination (Part I) for all candidates will be held in various cities of the United States and Canada on Friday, Feb. 6, 1948, at 2:00 P.M.

Applications are now being received for the 1948 examinations. Closing date for these applications will be Nov. 1, 1947.

For further information and application blanks address Paul Titus, M.D., Secretary, 1015 Highland Building, Pittsburgh 6, Pa.

PAUL TITUS, M.D.

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Mann, T.: Studies on the Metabolism of Semen. III. Fructose as a Normal Constituent of Seminal Plasma. Site of Formation and Function of Fructose in Semen, Biochemical J. 40: 481-491, 1946.

Mann, of Molteno Institute, Cambridge University, one of the foremost authorities on biochemistry of the semen, provides in this article most valuable documented information on the basic research concerned with reducible carbohydrate content of seminal plasma. He has established that, contrary to the views generally held, it was found that the reducing carbohydrate of the seminal plasma is not glucose but d (-)-fructose. This sugar has been purified from the seminal plasma and identified by its reducing value, optical activity, preparation of the methylphenyl-fructosazone, yeast fermentation tests, and other methods.

Mann found that fructose accounted for practically the whole of the yeast-fermentable reducing sugar in the seminal fluids of bull, ram, rabbit, boar, and human seminal plasmas. He was able to demonstrate little, if any, glucose in these specimens from the above species.

The author observed that the fructose level varied from one species to another, and even within the same species there were individual differences—providing clinicians with another possible clue in the evaluation of relative male infertility on the basis of hypo-fructose levels in the seminal plasma. In the bull, the highest levels were found: 1.0 Gm. fructose per 100 ml. seminal plasma.

Sperm obtained directly from the epididymis contained scarcely any fructose. This sugar is acquired by the semen from the accessory glands, principally the seminal vesicles. In certain animals not possessing these structures, notably the rabbit, the prostate was found rich in fructose.

C. E. FOLSOME.

Mann, T.: Studies on the Metabolism of Semen. III. Fructose as a Normal Constituent of Seminal Plasma. Site of Formation and Function of Fructose in Semen, Biochem. J. 40: 481-491, 1946.

The chief function of fructose in semen is to supply the spermatozoa with readily glycolyzable material. Stored seminal specimens show a progressive fall in the content of fructose and an accumulation of lactic acid.

The author concludes that normal spermatozoa utilize fructose, as this is the chief sugar available in seminal plasma, but their enzymic equipment enables them to metabolize equally efficiently glucose and mannose. The breakdown of these three sugars in sperm is initiated by a hexokinase interaction with adenosinetriphosphate. The subsequent metabolic degradation is through diphosphohexose, phosphotriose, phosphoglyceric acid, to pyruvic acid to lactic acid.

It is to be noted that Mann found the rate of fructolysis in semen was highly dependent on temperature. At 5° to 10° C. storage, an appreciable proportion of seminal fructose still remains after forty-eight hours' incubation, but at 30° to 37° C. the disappearance of fructose is only a matter of a few hours. Twelve excellently arranged tables document Mann's article.

C. E. FOLSOME.

MacLeod, John, and Summerson, William H.: The Phosphatase Activity of Human Spermatozoa, J. Biol. Chem. 165: 533-539, 1946.

The authors, at Cornell, aware that oxidation reactions in the sperm cell were secondary to those of sugar breakdown (glycolysis) determined to study the possibility of phosphate transfer as it might be of major significance to the metabolic processes in the cell. They investigated the metabolism of human spermatozoa in the presence of phosphate esters known to be of significance in carbohydrate metabolism in other tissues. Using washed sperm cells and evaluating with Warburg techniques they determined the effect of spermatozoa on adenosine triphosphate, adenylic acid (yeast and muscle), the various hexose mono- and diphosphates, Beta glycerophosphate and acetyl phosphate. While human spermatozoa did hydrolyze adenosine triphosphate to produce adenylic acid, other phosphate esters of recognized significance were not hydrolyzed under the same condition. In the former the hydrolysis did not modify the production of lactic acid from glucose by the cells. The liberation of phosphorous from the adenosine triphosphate was not accompanied by phosphate transfer, nor was any energy yielded by this reaction made available for the maintenance of motility.

C. E. FOLSOME.

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The American Board of Obstetrics and Gynecology in annual session at Pittsburgh, Pa., June 1 to 7, 1947, announces the election of the following officers:

Walter T. Dannreuther, M.D., President, New York City, N. Y.; Joseph L. Baer, M.D., Vice-President, Chicago, Ill.; Ludwig A. Emge, M.D., Vice-President, San Francisco, Calif.; Paul Titus, M.D., Secretary-Treasurer, 1015 Highland Building, Pittsburgh, Pa.; Norman F. Miller, M.D., Member of Executive Committee, Ann Arbor, Mich.

The other members of the Board are: Willard R. Cooke, M.D., Galveston, Texas; F. Bayard Carter, M.D., Durham, N. C.; Edward A. Schumann, M.D., Philadelphia, Pa.; and Robert L. Faulkner, M.D., Cleveland, Ohio.

Announcement

The American Board of Obstetrics and Gynecology in annual session at Pittsburgh, Pa., June 1-7, 1947, announced the following statement of policy:

It was never intended by this Board that certification should be required by any hospital as a prerequisite to appointment in various staff positions, even though certification or its full equivalent is considered a desirable requisite to appointment in key positions, as on the Senior or Chief Staff, especially of hospitals expecting to conduct approved services for training of residents.

This Board does not subscribe to any Hospital or medical school rule that certification is to be required for medical appointments in ranks lower than Chief or Senior Staff of hospitals, or Associate Professorship in Schools of Medicine, for the obvious reason that such appointments constitute desirable specialist training.

The Board also adopted certain changes in regulations as follows:

Candidates will be hereafter required to present not merely a fundamental knowledge of both branches of the specialty, but evidence of actual adequate training in obstetrics and gynecology.

Credit for graduate courses in the basic sciences which involve laboratory and didactic teaching rather than clinical experience or opportunities will be given credit for the time spent up to a maximum period of not more than six months regardless of the duration of the course.

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correlated with available clinical evidence, biochemical evidence and pathologic tissue studies, the interpretation of neoplastic growth propensities is greatly enhanced.

During the course of studying vaginal and cervical cytology smears for a diagnosis of uterine cancer, it was observed that a high percentage of our first two hundred cases proved to be cancer showed evidence of abnormally high endogenous estrogenic activity. This was first observed and reported by us in 1944.³ The observation assumed more than passing significance when a patient 70 years of age suffering from cervical carcinoma manifested a cytology picture of estrogenic cornification similar to that of a young woman in the regenerative phase of the sex cycle. The nature of the associated growth factor was confirmed in the proliferative pattern of the endometrium. Since this time all of our cancers have been studied carefully for evidence of estrogenic cornification using a special cytology technique which will be described later. Over 75 per cent of the cases have shown evidence of abnormal cornification, regardless of age.

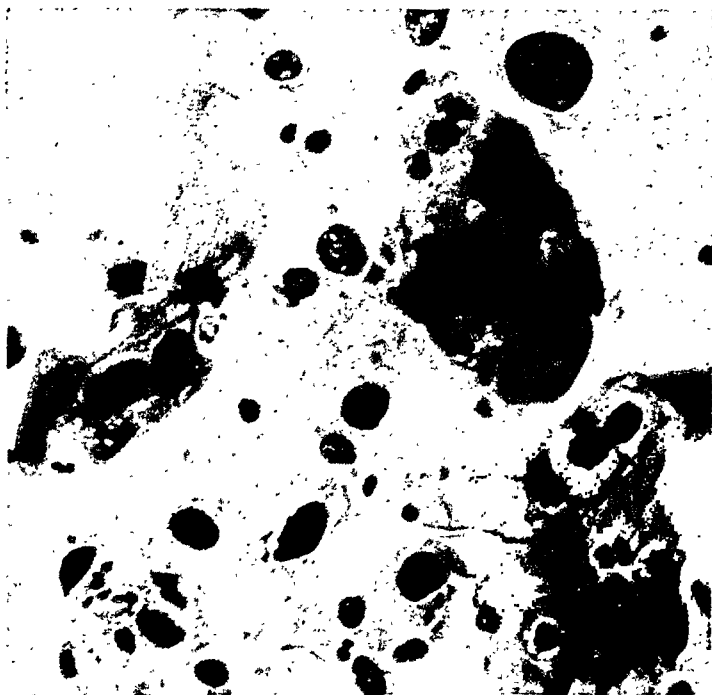


Fig. 1.—Cervical cytology smear in postmenopausal case of squamous carcinoma of cervix showing malignant cells and estrogenic cornified cells in close association. Note extreme nuclear variability in cancer cells.

Cytology studies have been made in over 3,500 cases, using a modification of the ingenious technique originated by Papanicolaou and Traut.⁴ It has become apparent that this method of study puts at the disposal of the medical profession a simple means of not only providing early uterine cancer diagnosis, but also of estimating the endogenous tissue estrogens of the body which may be causally related to the disease.

More recently, and almost by accident, we discovered the presence of a nutritional deficiency of thiamine to be frequently present in cases manifesting

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Original Communications

CERVICAL CANCER: A DISORDERED GROWTH RESPONSE TO INFLAMMATION IN THE PRESENCE OF ESTROGEN EXCESS AND NUTRITIONAL DEFICIENCY*

Cytological, Clinical, Nutritional, and Pathologic Studies

J. ERNEST AYRE, M.D., MONTREAL, QUEBEC

(From the Gynec-cytology Laboratory, Cancer Research Division, Department of Obstetrics and Gynecology, Royal Victoria Hospital, McGill University)

EVIDENCE that a type of human cancer is associated with a metabolic disturbance characterized by a nutritional deficiency, an estrogen excess, and an inflammatory reaction is herein presented. The inference is that uterine cervical cancer may be the abnormal type of inflammatory response to chronic infection which occurs in the presence of a nutritional deficiency of thiamine† and an associated excess of the specific growth-hormone estrogen.

Squamous carcinoma of the cervix is perhaps the type of cancer best suited for research investigation in humans. This type of cancer arises from a known localized focus, the squamocolumnar circle, according to such eminent pathologists as Novak,¹ TeLinde and Galvin² and associates. From this single spot, cancer originates more commonly than from any other known area in the human body! This area is accessible to the examining eye and finger, it is readily accessible for biopsy, its functions in health and disease are fairly well understood, and its reactivity to hormonal function is limited by tissue selectivity. The recent advent of the discovery of cytology techniques as a means of providing further information regarding cervical cell changes in association with changing estrogen levels and cervical infection provides what we believe to be a most significant addition to the surgical biopsy. While biopsies are seldom taken with great frequency, cervical cell-smears may be taken daily, and the morphologic nuclear changes found in the constantly exfoliating squamous cells provide fascinating evidence of growth activity. When these microscopic nuclear phenomena are

*Aided by a grant from Ortho Research Foundation.

†Thiamine indicates "Thiomine and/or Riboflavin" throughout paper.

and the relative levels of the excretion may be carefully assessed and compared in the pregnant and nonpregnant state. However, small variations in urinary estrogen in the nonpregnant state cannot be accurately assayed by the usual methods of study, and the urine represents only the excretion level which may not parallel the blood level. Heard⁸ states further that only approximately 10 per cent of any estrogen injected into the intact body is recoverable in the urine. The vaginal cornification count provides a simple method of obtaining a reasonably accurate estimation of endogenous tissue estrogens, although it does not give the biochemical differentiation between estradiol, estrone, and estriol. Cornification counts may be made in a similar manner to a blood count. It is well known from cytology studies reported by De Allende, Shorr, and Hartman⁹ and various other reliable investigators that the cornification level normally follows a cyclic pattern showing a rise from zero post menstrually, and rising gradually during the regenerative phase. There is evidence of slight day-to-day fluctuation which is probably dependent upon its variable production, metabolism, and excretion. A peak of cornification is reached at the ovulatory stage, and a physiologic drop occurs following ovulation. The curve during the secretory phase is somewhat more variable, but the usual premenstrual picture is one of very low or absent cornification.

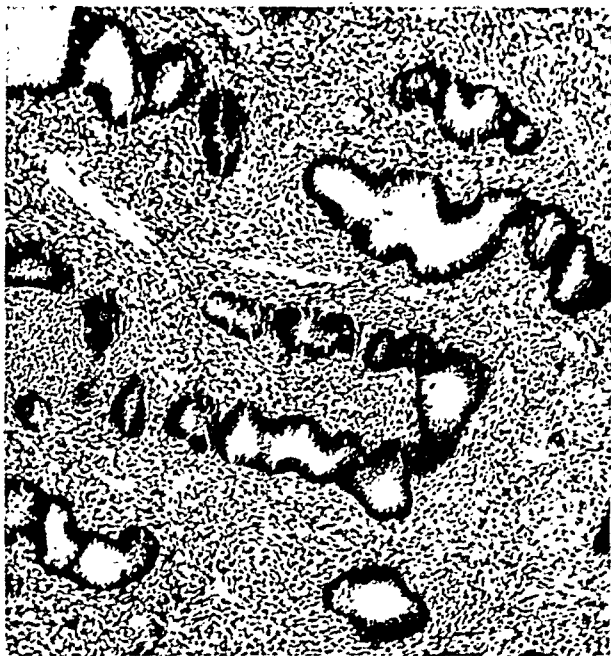


Fig. 3.—Endometrial biopsy in same case as in Fig. 2. The hyperactive proliferative pattern in a patient of this age confirms the presence of abnormally high estrogenic activity.

In humans and in monkeys the estrogens manifest their presence in the vaginal mucosa by a specific hormonal cornification change in the cells (first described by Allen,¹⁰ associated with proliferation of the vaginal and cervical squamous epithelium. This growth change is related to the deposition of glycogen in the squamous cell which is mediated and controlled by the force of the estrogenic stimulus. The vaginal epithelium of the average postmenopausal female is thin and is made up largely of basal cells which contain no glycogen, and cornification is absent. Under the influence of the estrogenic hormone the deposition of glycogen may be brought about and cornification of the squamous cells occurs whether the subject be post climacteric or following oöphorectomy. This was demonstrated in monkeys by Robertson, Maddux,

abnormal estrogenic cornification. The linkage of these two factors was first recognized by us in three cases which will be discussed in some detail. A preliminary report of our findings in these cases and in a small group of cases of known cancer and menorrhagia was recently made in *Science*.⁵ It is proposed in this report to present our findings and further observations on a series of 100 patients investigated from a combined nutritional, cytologic, clinical, and pathologic approach. Fifty of these were proved cases of cervical cancer, fifty were normal controls. Photomicrographs of some of the cytologic and pathologic evidence will be presented, and the results will be tabulated.

Studies of Endogenous Estrogen

Perusal of the scientific literature reveals considerable experimental evidence in animals to support a nutritional-hormonal relationship acting through the liver. Recent studies of liver function in dietary deficiency would appear to indicate impairment of this organ in its ability to inactivate estrogen. One

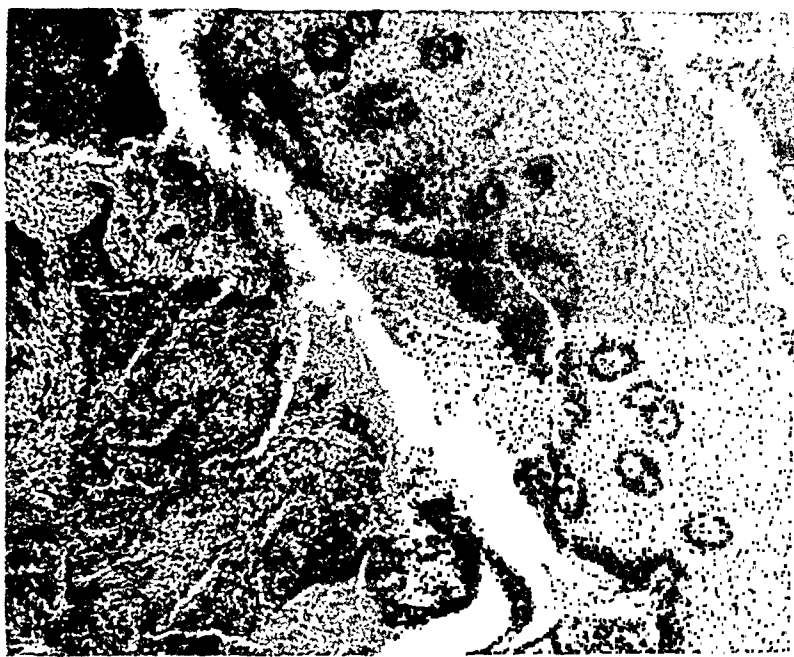


Fig. 2.—Biopsy of cervix. Note squamous epithelium adjacent to carcinomatous growth in patient 65 years of age. The cornified cells are evident on the surface. The depth of the squamous epithelium is indicative of active estrogenic growth stimulation. This picture is very much different from the thin atrophic epithelium found in normal postmenopausal cases.

wonders whether the human liver is similarly influenced in its function. If so, the urinary estrogens would vary appreciably with liver function as well as with ovarian production. While blood levels should give a true picture, most methods of determining this are complicated and unsatisfactory. There appear to be many unknowns in the metabolism of endogenous estrogen. Heard,⁶ who has investigated steroid metabolism intensively, states that we are still ignorant of the nature of the estrogen circulating in the blood. While the work of Venning and Browne⁷ has been successful in providing us with the means of accurate assay of corpus luteum activity by pregnandiol levels, urinary and blood estrogen levels do not yield to the same accuracy of assay. Analyzing the urinary excretions reveals some information in that three separate fractions, namely, estradiol, estrone, and estriol, have been demonstrated.

Equally convincing evidence that an estrogenic growth-stimulating factor is exerting its presence on the cervical epithelium is manifest in a study of biopsies of tissue adjacent to cancer growths (Fig. 2) in senile patients. The finding of a greatly thickened proliferative squamous epithelium with mature cornified elements at the surface is the same type of picture as may be induced by the administration of moderately large doses of an estrogen at any age, and is very much different from the thin atrophic epithelium found in normal post-menopausal cases.

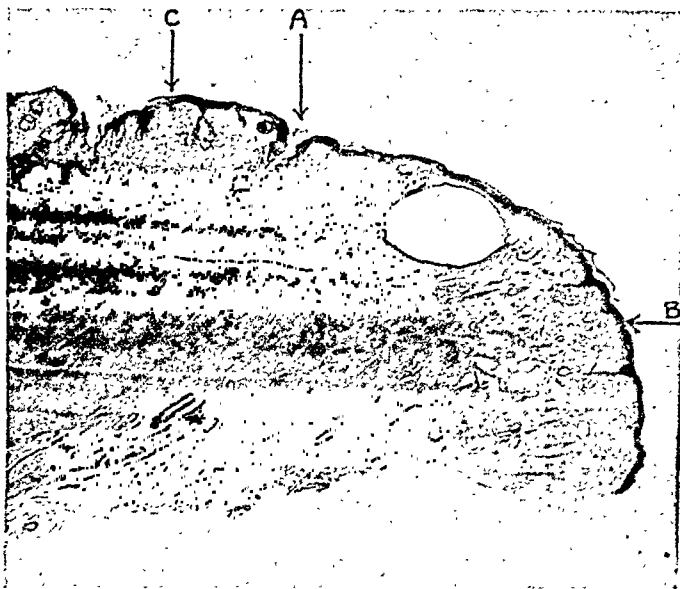


Fig. 4.—Cervical biopsy from young woman (30 years of age) complaining of intermenstrual bleeding. Pathologic diagnosis: cervicitis. Observe thickened squamous epithelium near glands which harbor infection.



Fig. 5.—(High power of Fig. 4, A). Squamocolumnar area in same case showing inflammatory exudate in tissues, and hyperactive thickened squamous epithelium adjacent to infected tissues and glands.

Recent advances in the field of radioactivity may prove valuable in verifying our cytologic evidence of tissue estrogen concentration. It is our hope to attempt to trace the course of radioactivated estrogens when suitable isotopes become available. That this procedure is distinctly possible has been

and Allen¹¹ and in humans by Krumm.¹² We have confirmed the latter's observations in our own laboratory. When the cytology smears are stained with the Papanicolaou¹³ stains (EA-50 and OG-6) using the technique perfected by him, the cellular picture is most colorful. The cornified cells stand out clearly and are recognized not only on the basis of their brilliant staining, but also on their morphologic characteristics. We have found further confirmation of the estrogenic activity by the study of the endometrium of senile patients suffering from cancer of the cervix. Many of these showing cornification in the smears also exhibited endometrium similar to that found in the regenerative phase in a young women (Fig. 3), while in other cases the estrogenic stimulus was sufficient to produce a picture of endometrial hyperplasia.

Studies of Cervical Tissue Estrogens

Our cytologic studies of the squamous epithelium of the cervix lead us to believe that this tissue reacts to the estrogenic hormones in a manner similar to that of the vagina, but with certain differences. The first and most significant is that this tissue exhibits a greater accentuation of the growth response induced by the estrogens. During the course of our cytologic studies we made the observation that the cervical cornification counts were found to be almost consistently higher than the vaginal cornification counts in the same cases. We had never been able to understand why this might be. During the course of a discussion, Dr. Edward C. Reifstein of Memorial Hospital, New York, suggested the likelihood that estrogen may become concentrated in certain specific tissues. At the time, we wondered whether this was the explanation for the higher estrogenic cornification counts in our cervical smears. Later, in studying the experimental work of Brunelli,¹⁴ we learned that in 1935 he had demonstrated that in rabbits estrogen present in the blood will become concentrated and fixed in inflamed tissues. This evidence suggests that chronic inflammation resulting from persisting infection in the cervical tissues might cause the concentration of estrogen in these tissues and thus account for the higher cornification counts. We therefore investigated comparative vaginal and cervical levels in a large series of cases, a report of which has been made elsewhere.¹⁵ From a series of 125 cases studied without regard to disease, 87 per cent were found to show higher estrogen counts in the cervical smear than in the vaginal, and the average difference was 15 per cent. The conclusion from this study was that concentration of endogenous tissue estrogens may occur in this organ. Whether the endogenous estrogens are concentrated more in the cervix than in the vagina in all women is uncertain. The high frequency of occurrence of chronic cervicitis has led us to attempt to correlate cervicitis with the concentration of estrogen in the cervical tissues. In our opinion, probably all parous cervices and many nulliparous cervices have been subjected to a degree of cervicitis at some time during sex life and some residual disease doubtless remains in the glands as a chronic cervicitis. Such estrogen constantly influencing these infected tissues would tend to produce constant growth proliferation. A study of cervical tissue biopsies confirms this growth feature. While peripherally the squamous epithelium shows less cornification and is thin, approaching the squamocolumnar junction, the estrogenic cornified cells are more numerous, and the epithelium becomes thicker with more evidence of proliferation in the basal epithelium (Compare Figs. 6 and 7). Since growth activity is most pronounced approaching the squamocolumnar junction, it seems probable that infection in the glands influencing the squamous epithelium adjacent may exert an effect on the glycogen-estrogen metabolism in these "inflamed" cells. This seems a most significant consideration, in view of the great frequency of chronic cervicitis as a precursor of squamous carcinoma.

between nutrition and hormonal activity in association with cervical cancer. These patients were aged 14 years, 29 years, and 64 years, respectively. They were first studied in our gyne-cytology laboratory, all three of them showing abnormally high cornification during a bleeding phase. In addition, they presented other significant cytologic features. In view of the abnormal dietary habits revealed by their histories, urinary levels of the various vitamin fractions were undertaken. These have demonstrated low thiamine levels in all cases, while the other vitamin fractions were normal. A discussion of these cases individually follows:

CASE 1.—The patient, Mrs. M., aged 29 years, a nulliparous white woman of Anglo-Saxon extraction, was admitted to the hospital with complaints of severe menorrhagia of three months' duration, her periods usually lasting ten

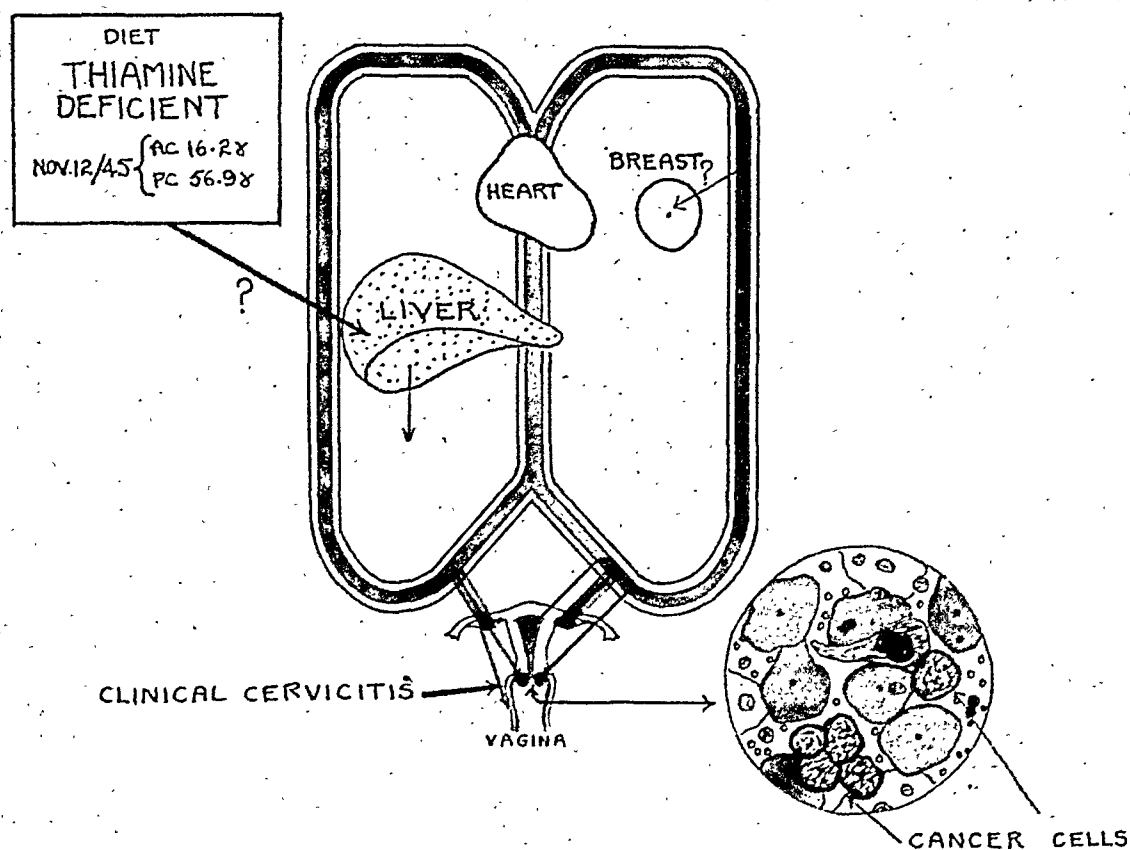


Fig. 8.—Human findings in early cervical cancer. Diagrammatic representation of diet-liver(?)—estrogen findings in Case 1 of early cervical cancer.

to fourteen days, with some intermenstrual spotting. She complained also of chronic constipation and severe abdominal cramps, aggravated by the taking of solid food, which at times produced nausea and vomiting. As a result the patient has been existing chiefly on soft foods and liquids, and stated that mineral oil was the only laxative she could take to stimulate intestinal action without inducing pain. It was revealed that she had for years partaken heavily of alcoholic beverages. In view of her obviously inadequate diet, it was felt that investigation should be made to determine a possible correlation between a nutritional deficiency and the severe menorrhagia. Pelvic examination revealed a normal-sized uterus with an inflammatory cervical erosion. Cervical cytology smears revealed two findings of note—the first a high cornification

shown by the work of Belanger and LeBlond,¹⁶ and of others. Proof of fixation in the infected cervix will not only incriminate the growth-stimulating estrogens, but may offer better hope for successful treatment of cancer. The destructive rays given off selectively, where concentrated, might kill the sensitive neoplastic cells while undergoing mitotic division.

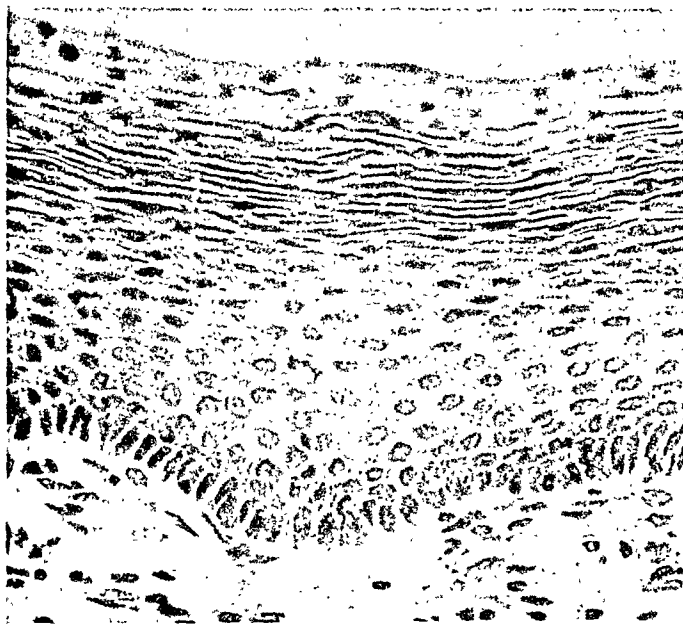


Fig. 6.—(High power study of Fig. 4, B). Biopsy of cervix peripherally, showing normal degree of proliferation.

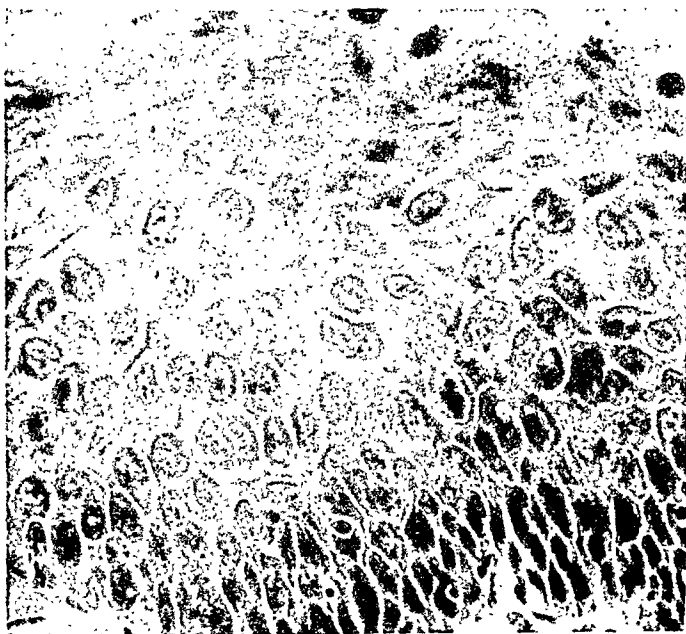


Fig. 7.—(High power study of Fig. 4, C). Biopsy of cervix approaching squamocolumnar junction in same case. Observe striking contrast in proliferative activity in region of infection. Cervical tissue estrogens excessive in cervical cytology smear. Note marked squamous hyperplasia with some loss of cell polarity.

An interesting correlation between thiamine deficiency, high estrogen levels, and gynecologic bleeding has recently been made in the three test cases referred to. This has led to investigation of a possible etiologic linkage

Postoperatively, cytology smears continued to reveal profuse exfoliation of the malignant appearing cells.

Following consultation and discussion, a conservative course was decided upon, and the patient was merely subjected to a high cervical amputation. This very conservative surgery was performed with the intention of doing a panhysterectomy at a later date if any further evidence of malignant activity could be detected clinically or in cytology smears. Following the amputation of the cervix, smears have been taken regularly and at no time have atypical cells again been detected.

It is interesting that with no further treatment other than correction of her diet and bowel habits, and the administration of supplemental thiamine therapy orally, this patient has resumed a normal menstrual habit since the operation twelve months ago. While cytologic tests continue favorably, she is being followed assiduously with the intention of receiving further treatment with radium or surgery if indicated.

CASE 2.—Our first contact with this patient was made when her personal physician brought in cytology smears for a diagnosis of possible malignancy. He reported that his patient, a Jewish woman, 64 years of age, had recently noted a bloody vaginal discharge of two days' duration. She had had her normal menopause fourteen years previously. Study of the cytology smears showed malignant cells of the squamous type. In addition to this finding, the percentage of estrogenic cornified cells was abnormally high (42 per cent). On the basis of the patient's history, and the cytologic diagnosis of cancer, the patient was referred to Dr. W. A. G. Bauld, Chief of our Gynecologic Cancer Service.

On admission, examination revealed a well-nourished female with no complaints other than the history as given. Pelvic examination revealed a small indurated ulceration of the cervix which, from clinical evidence alone, aroused only a suspicion of malignancy to the experienced eye of Dr. Bauld.

Before any treatment was undertaken, the following biochemical estimations were made. The Nutrition Department reported urinary thiamine excretion as follows: ac-36.4, pc-94.8.

Biochemical examination gave the following results: nonprotein nitrogen 23.8 mg. per cent; total protein 5.6 mg. per cent; albumin 4.18 mg. per cent; globulin 1.42 mg. per cent; cephalin flocculation, negative; alkaline phosphatase, 4 units; bromsulphalein, 10 per cent retention; glucuronic acid, 3.85 mg. per cent of glucurone.

At operation, a confirmatory biopsy was taken and 4,800 mg. of radium were administered. The biopsy proved to be a squamous carcinoma of the cervix of a highly undifferentiated type.

In view of the low thiamine excretion level, the patient's dietary habits were investigated. It was revealed that while her financial status was good, her diet was average with the exception that very little meat was eaten and she admitted constant dieting to prevent overweight. The dietary analysis confirmed the inadequate thiamine intake.

CASE 3.—The patient, Miss N., aged 14 years, was a child of French-Canadian extraction, admitted to the hospital with the complaint of profuse vaginal bleeding of two months' duration. She had had her first menstruation at the age of 13 years, following which she had a period of amenorrhea of one year. A second menstruation occurred in August, 1945. She again started to bleed in October and this was continuous for two months, at times being quite profuse, and necessitating bed rest for two weeks prior to admission. Examination showed a frail anemic-appearing child, weighing 90 pounds, with slight breast development and incomplete growth of pubic hair. A striking feature

level, the cornification count being 75 per cent, but second, and more startling, large numbers of cancer cells were also found.

At this time, estimation of urinary vitamin levels were reported by the Nutrition Department as follows: riboflavin—ac-188.4 (normal 165), pc-445.9 (normal 250); thiamine—ac-16.2 (normal 25-50), pc-56.9 (normal 200).

Further biochemical examination gave the following results: nonprotein nitrogen 22.6 mg. per cent; total protein 7.56 mg. per cent; albumin 4.92 mg. per cent; sugar—ac-111 mg. per cent; pc-105 mg. per cent; bilirubin—direct 0.3 mg. per cent, indirect 0.8 mg. per cent.

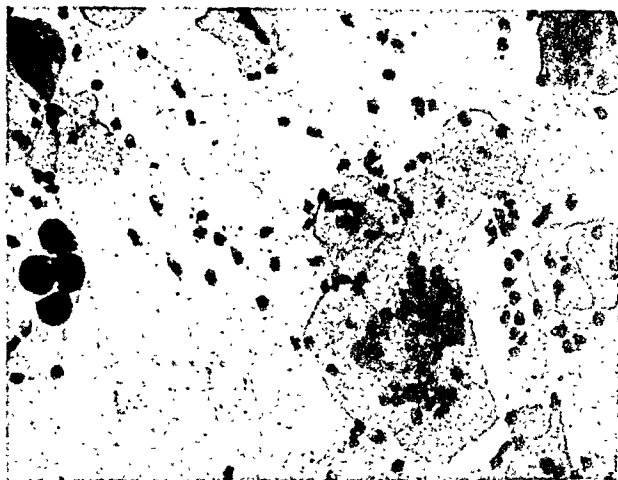


Fig. 9.—Cervical cytology smear (low power) of Mrs. M. (Case 1), showing excess estrogenic cornification count, cluster of neoplastic cells, leucocytes, and blood.

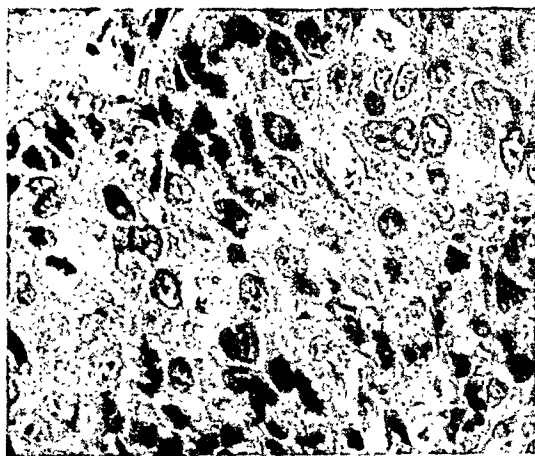


Fig. 10.—Cervical biopsy in Case 1 showing intra-epithelial carcinoma of cervix. This noninvasive lesion was invisible clinically. Patient showed cervicitis, high tissue estrogen (Fig. 9) and low thiamine etc., as represented diagrammatically in Fig. 8.

Liver function tests showed: hippuric acid 1.3832 Gm.; bromsulphalein 2.4 per cent retention; cephalin flocculation—24 hours (+2), 48 hours (+2).

Blood examination revealed: hemoglobin 70 per cent; white blood count, 8,800/cu.mm.; sedimentation rate 40 (28 C.V.), compact cells 31.6 per cent.

Cervical biopsy for confirmation of diagnosis was undertaken. In view of the inability to detect any visually demonstrable lesion, several biopsies were taken and the uterine cavity was curetted. Following a study of serial sections of the biopsies, a localized carcinoma-in-situ was revealed.

Singher, Kensler, Taylor and others¹⁹ reported their observations of liver inactivation of estradiol when the following specific deficiencies were produced, viz., thiamine, riboflavin, pyridoxine, pantothenic acid, biotin, and vitamin A. Using liver slices of rats and mice, their observations indicated that estradiol inactivation by the liver depends on the liver content of riboflavin and thiamine. The levels of pyridoxine, pantothenic acid, biotin, and vitamin A in the liver had no influence on the inactivation of this estrogen. They concluded that thiamine and riboflavin are essential in the metabolism of estradiol by liver slices, and they state that it seems possible that these vitamins may be involved in estrogen metabolism through their role as members of an oxidative enzyme system. Zondek²⁰ reported that the liver is capable of inactivating from 80 per cent to 90 per cent of added estrogen in vitro.

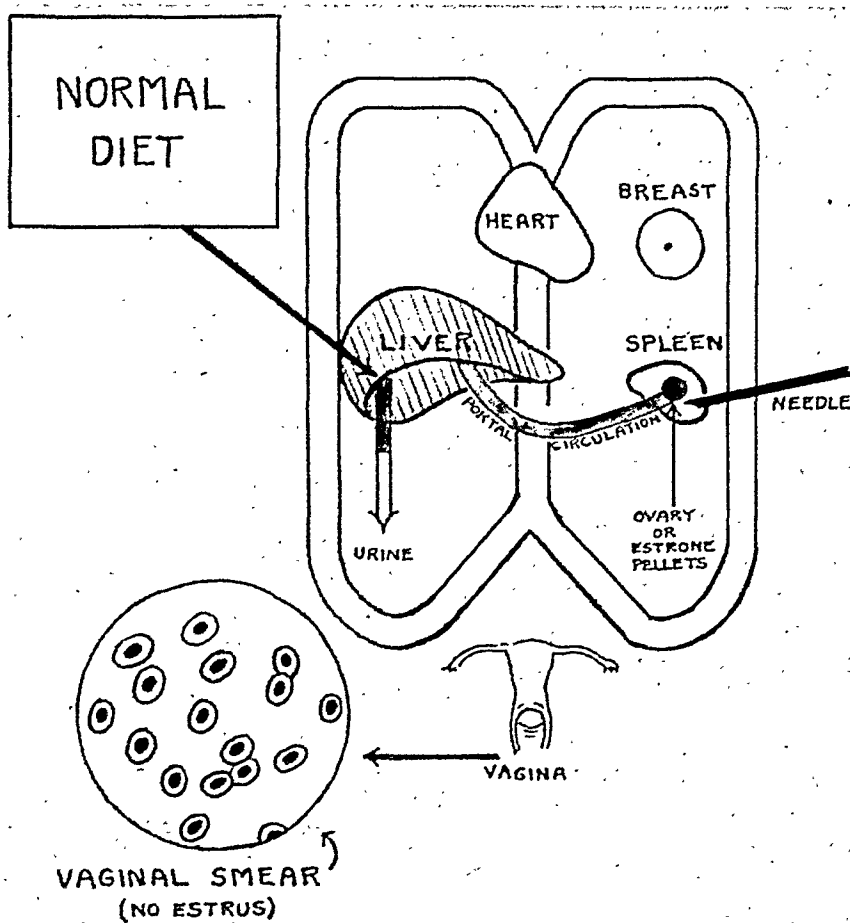


Fig. 11A.—Experimental intrasplenic estrogenic administration to castrate female rats. Diagram illustrating experimental evidence of nutrition-liver-estrogen inter-relationship in animals. Estrogen from the spleen enters portal circulation travelling direct to the liver. In Fig. 11 A with normal liver function the liver inactivates the estrogen and no estrus develops.

Golden and Sevringhaus²¹ transplanted rat ovaries to the mesentery and to the axillae. Estrus did not occur in animals with ovaries in the portal circulation, but did occur in those with transplants in the axillae.

Talbot²² extended the observation of Golden and Sevringhaus²¹ on destruction of endogenous estrogen by demonstrating that a liver poison, carbontetrachloride, can impair the estrogen-inactivating mechanism.

It has been recognized that menorrhagia and metrorrhagia may occur early in the course of cirrhosis of the liver,²³ and the work of Gyorgy and Goldblatt,²⁴

was noted in that the gums were toothless, a total dental extraction having been performed for dental caries two months previously. Pelvic examination revealed that the hymen was intact and the pelvic organs normal, though with an infantile tendency.

Following bed rest in the hospital there was no apparent diminution in bleeding.

Daily vaginal cytology smears were taken, showing a persisting high cornification plateau with clusters of endometrial appearing cells and considerable blood.

Biochemical examination gave the following results: Nonprotein nitrogen 20.4 mg. per cent; total protein 6.18 mg. per cent; albumin 4.02 mg. per cent; globulin 2.16 mg. per cent; bilirubin—direct 0.225 mg. per cent, indirect—0.55 mg. per cent.

Liver function tests showed bromsulphalein 2.4 per cent retention; cephalin flocculation 24 hours—negative, 48 hours—negative; hippuric acid 1.5115 Gm. Blood examination showed: hemoglobin 65 per cent; sedimentation rate—first hour 25 (C.V.9); white blood count, 8,900 per cu.mm.; prothrombin time, 36 seconds. Riboflavin was ac-190.0, pc-330.7. Thiamine was ac-11, pc-51.

This patient was treated further by having a curettement following completion of her biochemical studies. At the time of the operation, the pelvic organs were found to appear normal. When the uterine cavity was explored, a large quantity of thick endometrium was evacuated, and parts of this appeared to be grossly firm and polypoidal. Following operation, the patient was placed on large daily doses of thiamine.

Pathologic study of the tissue removed showed numerous endometrial polypi with marked glandular hyperplasia and slight cystic change in evidence. Parts of the gland tissue presented an appearance of growth of an adenomatous character. Indeed, the pattern was such that if the patient had been 40 years of age instead of 14, the tissue would have been considered carefully before dismissing borderline malignant change.

This patient has resumed a normal menstrual cycle during the past eighteen months on a corrected dietary regime supplemented by adequate doses of vitamin B complex.

Liver Studies in Animals

Certain evidence has already been presented in animal studies to show that liver damage sufficient to interfere with the excretion of the estrogens does occur.

Biskind and Biskind¹⁷ reported that vitamin B complex deficiency interferes with estrone inactivation in the liver in female rats. They implanted pellets of estrone in the spleens of adult castrated female rats. The estrone must pass directly to the liver by way of the portal circulation before reaching the systemic circulation. While these animals were fed a normal stock diet, no estrus developed. When the diet was changed to one totally deficient in vitamin B complex, it was observed that within two weeks on this diet, irregular estrual changes began to occur. This was interpreted as indicating that the estrone was not being completely inactivated, and after three weeks on this diet, the rats remained in a state of constant estrus.

Since this time numerous investigators have confirmed the observations of Biskind and Biskind.¹⁷ Segaloff and Segaloff¹⁸ found that a deficiency of the B vitamins decreased the ability of the rat's liver to inactivate estrone, alpha-estradiol, and diethylstilbestrol, as indicated by an increased vaginal response to intrasplenically-injected estrogen. When either thiamine or riboflavin were administered in large doses, the rate of inactivation of estrone and alpha-estradiol (but not of diethylstilbestrol) returned to a normal level.

great secretion of estrogen leading up to the time of ovulation. Its effect is also specifically exerted upon the squamous epithelium of the vagina, and a comparable manifestation of growth may be observed in this tissue coincident to the endometrial changes. The uterine cervix is covered by the same type of epithelium and reacts to the same growth stimulus, and this is the tissue most commonly involved in cancer in the human female.

Pincus and Graubard,²⁷ in studying estrogen metabolism in seven women suffering from cancer of the uterus, concluded that these cases metabolized the estrogen in an abnormal manner. While noneancerous women showed a definite increased total estrogen output (in the urine) following administration of estrone plus progesterone, the cancer cases showed a negligible increase in the urine after the same treatment. The fact that the estrogen was not excreted the same as in a nonmalignant case suggests more profound liver impairment.

The administration of estrogens to certain animals has been followed by the development of various types of neoplasia.

A recent survey of evidence of estrogenic activity in 62 granulosa-cell tumors has been made by Hodgson, Dockerty, and Mussey.²⁸ They cite "evidence of hyper-estrinism is afforded in our series by symptoms of precocious puberty, amenorrhea, and postmenopausal bleeding" and observed that "urinary assays performed in the case of a woman, aged 57 years, were positive for eight rat units of estrogen per liter of urine excreted during the first twenty-four postoperative hours. The excretion of estrogen dropped to zero during the next twenty-four hours. Blood and urine assays should be performed in these cases both preoperatively and postoperatively to widen our information concerning the excretion of estrogen as well as to aid in clinical diagnosis." They reported proliferative endometrium in 67 per cent of their cases. In thirty-eight postmenopausal patients who had granulosa-cell tumor they reported 21 per cent as showing endometrial carcinoma and, in almost one-third of these cases, carcinoma of the breast with axillary metastasis also developed. They concluded that "this phenomenon of coexistent ovarian endometrial and mammary carcinoma in the human being bears a marked similarity to the results of experiments on laboratory animals in which estrogen stimulation appears to be a factor in carcinogenesis."

In animals it has been found that the implantation of ovarian tissue produced cancer of the breast in cancer-susceptible mice and it was felt that some secretion of the ovary played a role in the production of cancer. For a long time it has been recognized that certain coal tar products produced cancer with greater certainty than any other known chemical or physical irritant. The chemical structure of such substances has been found to contain benzene rings linked together. Certain active substances were found in the sex hormones, the bile acids, and in cholesterol exhibiting a similarity in structure to the coal tar preparations.

Rhoads²⁹ has presented evidence to show that in rats the administration of one of these two-benzene-ring substances, "butter yellow" will result in the development of cancer when their diet consisted of polished rice and carrots. It was found that if liver or yeast was added to the basal diet, no cancer occurred. Here, clearly, was an experiment in which a dietary constituent, rich in its content of the vitamins of the B complex, was protective against induced cancer. In studies of the vitamin B content of cancer tissue, it has been shown that the tissue of human, as well as of mouse carcinoma, is low in its content of vitamin B. This was reported in 1929 by Jackson and Kranz.³⁰

Extensive studies on numerous experimental animals, including monkeys, indicate that prolonged and not necessarily excessive administration of estrogens may produce changes in the epithelial structures which they normally stimulate.

and of others has demonstrated that cirrhosis of the liver is known to result from nutritional deficiency. Sources of the B complex have been shown to protect the liver against a variety of toxic agents such as lead, arsenic dimethylanilazo-benzene, which cause functional and morphologic damage to this organ. In addition to this evidence, Goldberger²⁵ has shown that menorrhagia may occur in pellagra.

In 1940, Glass, Edmondson, and Soll²⁶ reported that in male patients with cirrhosis of the liver the estrogen in the urine appeared in active form. Gynecomastia and testicular atrophy were associated with the excess of free estrogen.

Estrogen as a Carcinogen

Whether or not the accumulation of uncertain quantities of estrogens in the body would act as a carcinogen to the estrogen-susceptible tissues of the Müllerian tract and possibly the glands of the breast, is worthy of consideration.

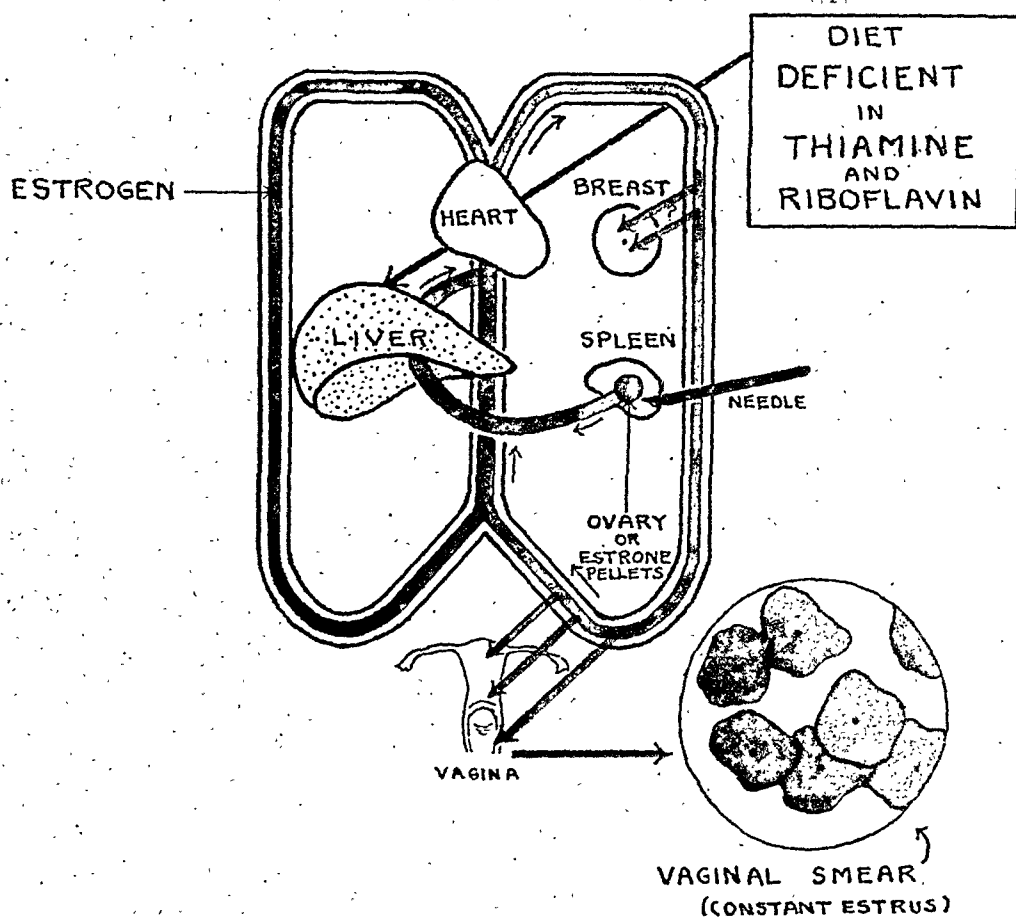


Fig. 11 B.—Experimental intrasplenic estrogenic administration to castrate female rats. Diagram illustrating experimental evidence of nutrition-liver-estrogen interrelationship in animals. Estrogen from the spleen enters portal circulation travelling direct to the liver. In Fig. 11 B constant estrus develops.

References: Biskind, M. S., and Biskind, G. R.: *Endocrinol.* 31: 109, 1942. Segaloff and Segaloff, *Endocrinol.* 34: 346, 1944. Singher, H. O., Kensler, C. J., Rhoads, C. P., et al., *J. Biol. Chem.* 154: 70, 1944.

It is known that estrogen is essentially a growth-promoting hormone affecting the uterine and vaginal tissues and, to a lesser extent, the mammary gland. During a normal cycle the endometrium manifests the most rapid physiologic proliferation during the follicular phase under the influence of an increasingly

The results of thiamine and riboflavin tabulated in the charts below are taken in each case from the pc. reading.

3. *Liver Function Tests.*—Through the cooperation of Dr. M. M. Hoffman, liver function tests were attempted in those cases who were available for this type of investigation. Unfortunately, the number of patients undergoing this study was small, and the results are therefore inconclusive. The cephalin flocculation test and the bromsulphalein tests showed more consistently abnormal readings than other liver tests.

4. *Urinary Estrogens.*—Urinary assays of estrogen were attempted in a few cases. Most of the patients, however, were not readily available for this type of study, and it was felt inconclusive to attempt these arduous studies without adequate control over the subjects. For accurate studies the entire urinary output over a considerable period of time would require analysis, and a single 24- or 48-hour quantity would not be conclusive.

Nutritional Studies

It perhaps seems remarkable in these days of scientific enlightenment and dietary refinement that deficiency would occur irrespective of the economic status of the patient. It has long been a general feeling among gynecologists that dietetics were not directly concerned with the production of pelvic pathology, and that the need for vitamins in particular was generally overstressed. It would seem logical that the average person with a normal appetite for the various staple foods should not develop a deficiency due to an inadequate intake. A study of thiamine physiology and metabolism reveals evidence to indicate that this substance would appear to be particularly vulnerable to intermittent or chronic depletion without gross deficiency in the diet as a whole. This tendency would appear to depend upon the fact that little thiamine is stored in the organism, and the amount is only sufficient to maintain proper life for a few days. A daily intake of thiamine is necessary, and the organism absorbs only enough for the immediate needs. The excess is destroyed or excreted. More is required when a high carbohydrate diet is taken or when alcohol is imbibed. We have found that a vicious cycle may develop as anorexia and constipation frequently develop in the presence of even a mild deficiency. Therefore, the more persistent the anorexia, the more chronic the deficiency becomes.

This vicious cycle would appear to be of more than passing importance. A discussion of dietary habits with some of our patients found to have a low thiamine excretion level has proved most illuminating. Some of these patients when questioned have admitted a diet consisting of tea and toast and potatoes, and when asked why they did not eat more, they indicated that they had no appetite and had almost to force themselves to eat what they did. Chronic constipation is consistently present and loss of weight has not been uncommon. Chronicity appears to be the rule once these patients slip into this rut. In an effort to determine whether the thiamine excretion level may have been only a transient deficiency, repeat tests have been done from month to month on certain cases without alteration of diet. These cases have most consistently shown a persisting low level over a period of several months. On the other hand, by simple correction of diet, the excretion levels have been normalized within an interval of seven days. The majority of these patients have not exhibited the appearance of undernourishment. On the contrary, most of them were a little overweight and, in addition, showed a lowered basal metabolic rate. Indeed, many of the patients admitted constant dieting in an effort to keep their weight down. This usually signifies a low fat intake which would seem to be one of the possible reasons why such patients would develop the thiamine deficiency, as the lower the fat intake, the greater becomes the body requirements of

that is, mammary, endometrial, and cervical epithelia, which vary from benign hyperplasia to definite malignancy.

Gemmel and Jeffcoate,³¹ in 1939, reported three cases of carcinoma of the cervix in a series of more than forty cases of senile vaginitis and kraurosis vulvae treated with estrogens.

Auchinloss and Haagensen³² in 1940 reported a case of mammary carcinoma with axillary metastasis in a woman treated for menopausal symptoms for over a year with moderately heavy doses of estradiol benzoate. They believe that in this case the cancer was probably produced by the estrogen in a woman with a definitely bad family history.

J. S. Henry,³³ in a recent extensive survey of the role of estrogen in carcinogenesis, reports two cases of endometrial overgrowth of a malignant or pre-cancerous nature in women who had taken an estrogen continuously over a prolonged period of time. He considers it probable that the changes found in these cases were produced by the estrogen therapy, and wisely counsels that prolonged or excessive administration of these hormones in practice should not be undertaken without careful consideration and knowledge of their potentialities. From the evidence presented, it would appear that the administration of estrogen may be harmful in those cases where obscure liver damage might have followed a dietary deficiency or some other damaging influence.

Method of Investigation

1. *Cytology*.—Cytology tests were taken from the cervix using the method described by Ayre and Dakin.³⁴ The secretions aspirated from the external os of the cervix presented evidence, first, as to the diagnosis of cancer, and second, by careful cornification counts of the cellular elements, endogenous estrogen levels were assayed. In those cases of advanced carcinoma, and in the cases of hemorrhage where the quantity of blood or purulent material obscured the cornified elements, a special technique was used for the cornification estimation. Using a speculum, a small spatula was employed to scrape the smooth mucosal surface of the cervix peripheral to the growth, thus avoiding the thick admixture of mucus, leucocytes, and blood on the surface of the growth and covering the vaginal floor. This permitted, we feel, a more accurate estimation of the estrogenic cornification. The fifty cases of cancer in this present investigation were studied using this technique while the preceding 150 odd cases were studied using the older method. We feel that this improved technique accounts for the higher percentage found to exhibit abnormally high cornification levels. The spatula technique has proved invaluable in the diagnosis of microscopic cancer, as the cells exfoliated precisely from the squamocolumnar junction may be scraped up in this selective fashion and smeared on the slide. This new technique has been described elsewhere.³⁵

2. *Nutrition*.—The nutrition studies were made by Dr. W. A. Andreae of the Nutrition Department of the Medical Laboratory of McGill University Clinic. It is noteworthy that the biochemists in the Nutrition Department had no knowledge or information of which specimens were from cancer cases, and which were from controls, before the results were computed. The vitamin status in the present investigation was estimated by a vitamin tolerance technique. Following a vitamin-free supper, the night urine from 12 midnight to 8 A.M. was collected in a bottle containing acetic acid. In the morning, after a vitamin-free breakfast, an intramuscular injection of 1 mg. thiamine and 1 mg. riboflavin was given and the urine collected for the subsequent four-hour period. Both specimens were analyzed—by the thiochrome method of Wang and Harris³⁶ for thiamine, and by the Ferrebee method³⁷ for riboflavin. Patients with below normal excretion values were classed as deficient in thiamine and/or riboflavin.

Abnormal endogenous estrogenic activity has been interpreted by cornification counts in vaginal and cervical smears. The degree of abnormality represented by plus or minus takes into consideration the age of the patient and the stage of the menstrual cycle. Whether the cornification count is slightly elevated above normal, or is marked, is indicated by degrees, viz., one, two or three plus. "N" represents normal expectations, and minus represents a lower than normal cornification level.

Analysis of Results

Chronicity or variability of all three factors under consideration must be borne in mind. The infection is chronic and probably does not vary appreciably from month to month. Blood estrogens normally are believed to vary in a cyclic fashion. This may be greatly changed by liver dysfunction. Tissue estrogens, on the other hand, may be more constant due to fixation. Thiamine excretion might be expected to vary with the diet. While the intake of thiamine in the diet of most people would tend to show some variation from week to week,

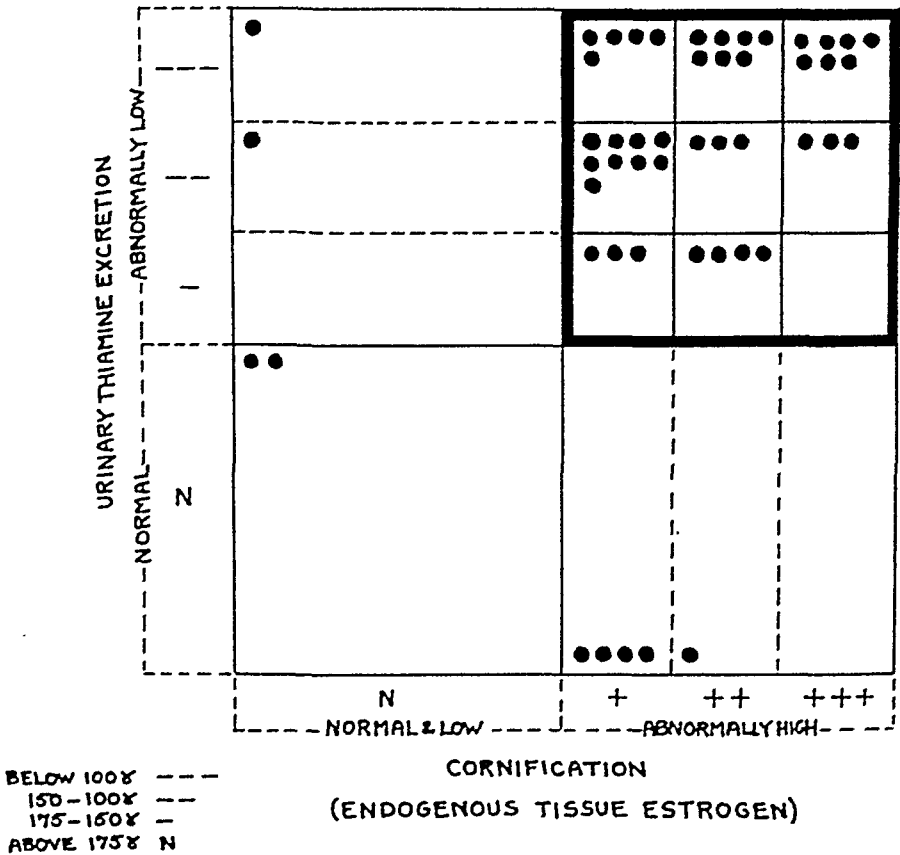


Fig. 12A.—Graphic representation of thiamine-estrogen findings in 50 cancer cases.

dietary habits and errors of habit do show a tendency to chronicity, and, as we have indicated elsewhere, once these patients have slipped into the rut of deficiency, the vicious cycle resulting may tend to keep them there, and in the patients on whom repeat levels were taken over a period of months, chronic deficiency was demonstrable. The tissue estrogens might also tend to show some variation. Primarily, the blood estrogen level, and secondarily, the urinary and tissue estrogens, would depend upon variable production, metabolism, and excretion. According to our presently discussed evidence, the metabolism and excretion might vary with the diet and liver function, and also with infec-

thiamine. Therefore, it would seem that two different types of dietary errors might predispose to thiamine depletion—those who are living on sweets and starches, and those who are constantly dieting to prevent or minimize obesity.

Thiamine is a water-soluble substance which is absorbed in the small intestine and is partly secreted in the gastric juice. It is stored in certain organs, namely, the kidney, liver, and heart, in small but variable amounts. It seems surprising that pork muscle contains eight times as much as beef.

Thiamine is important in carbohydrate metabolism. Glycogen requires its presence to be properly metabolized. Thyroxin secretion increases general metabolism and therefore necessitates an increased amount of B₁. The thiamine requirements are variable. More is needed in pregnancy, in hard physical labor, or with increased metabolism. A diet rich in fats reduces the amount of thiamine needed. In general, the daily minimal requirements are 50 to 300 international units.

A deficiency of thiamine can be accurately detected by measuring the amount excreted in the urine. A normal person excretes 100 micrograms per day.

With so much discussion of vitamin therapy nowadays, one might be led to believe that they are a "cure-all." The truth, however, is that vitamins are only nutritional elements, and to say that a vitamin would cure a deficiency or a disease resulting from a deficiency, is simply to say that a well-balanced diet, properly absorbed and utilized, would have prevented the disorder.

Results

A group of 100 gynecologic cases manifesting evidence of malignancy or normalcy have been studied cytologically for evidence of estrogenic activity in the gyne-cytology laboratory and nutritionally by thiamine excretion assays performed in the Nutrition Department of the Medical Laboratories of the McGill University Clinic. The series is made up of 50 cases of cervical cancer. Fifty controls were studied concurrently by similar vitamin-hormone assays. These controls were selected on the basis of normal gynecologic health, both subjectively and objectively, patients of a similar age group to the cancer series being selected wherever possible. The results have been shown graphically in Table I.

TABLE I

| | HIGH CORN. LOW THIAM. | HIGH CORN. | NORMAL AND LOW CORN. | NORMAL THIAM. | LOW THIAM. |
|-------------|--------------------------|------------|-------------------------|------------------|---------------|
| 50 Cancer | 82% | 92% | 8% | 14% | 86% |
| 50 Controls | 0 | 6.2% | 94% | 90% | 10% |

Results of Riboflavin Estimations

| | |
|---|-------|
| Total number of cases studied | 100 |
| % of cases having riboflavin test | 80% |
| % of low riboflavin in 38 cases of cancer | 36.8% |
| % of low riboflavin in 42 control cases | 6.8% |

Explanation

The thiamine excretion level used by Dr. W. A. Andreae of the Nutrition Laboratory to denote deficiency of thiamine is 200 α during the four-hour period following the injection of the 1 mg. test-dose of thiamine parenterally. For the purpose of this investigation 175 α has been chosen as the arbitrary level for normals in order to eliminate borderline cases. In the majority of the cases, riboflavin levels were also investigated. It is unfortunate that lack of adequate laboratory assistance made it impossible to measure this function in all cases.

The thiamine deficiency may also exert a dual role, acting on the liver, but also acting locally upon tissue cells in such a manner as to affect the metabolism and growth character of the individual cells of the cervix.

The fact that thiamine deficiency exists does not per se imply that the estrogen will be high and, therefore, that a cancer-potential exists. Ten per cent of the controls were thiamine deficient but they did not show high estrogen. This confirms that estrogen production is independent of the nutrition status, except possibly in acute starvation where menstruation and ovarian function may cease. This suggests, too, that the absence of the estrogen might nullify the neoplastic hazard.

It must be remembered that the cases we have analyzed have not been starvation victims, but rather, mild, probably chronic deficient. A statistical survey of cancer incidence in Europe during the next few years might yield valuable information if the machinery were available to collect accurate records.

Whether the low thiamine levels signify a pure deficiency of this nutritional element, or whether they signify a more general nutritional deficiency state of which the low thiamine is only an indicator we cannot be certain. Some evidence points to a pure thiamine deficiency. Most of our cases analyzed for vitamin A and vitamin C levels have shown normalcy in these respects. While our riboflavin results are incomplete, those available, which include 80 per cent of our series, tend to indicate that riboflavin occupies a secondary position in frequency of depletion and probably also in velocity to thiamine. While the majority of cases have shown a mild or moderate thiamine deficiency, usually only the moderate or severe cases have revealed a drop in the riboflavin level. Of our total series of cancer cases, 36.8 per cent have been shown to be deficient in this vitamin factor. In attempting to correct thiamine and riboflavin deficiencies by improved diet alone, our cases have shown further that the thiamine level is recovered more quickly than the riboflavin.

Chronicity is an unknown factor, but recent findings in early microscopic cervical cancers point to a long period of development, probably several years. Most people develop a fixed habit of diet, and a dietary error over a period of time would tend to produce a chronic deficiency. Chronicity would seem to be the rule, too, in regard to the infection and to the persisting estrogen stimulation.

While there are still many unknowns in the enzymic activity of thiamine and riboflavin as related to body and tissue metabolism, liver function and estrogen metabolism, the frequency of the reported combination of findings would appear to be more than coincidental. It has long been recognized that chronic irritation is a contributing factor leading to the development of many types of cancer. It is accepted knowledge that infection alone will not produce a malignant growth without the addition of other unknown factors. It would appear that both nutrition and estrogen have a role to play. Undoubtedly, the precise intensity, chronicity, and selectivity of all three elements must exert a fundamental force upon body tissue and cell metabolism, and these factors are still obscure.

It was mentioned in the previous publication⁵ that even while the thiamine-estrogen hypothesis was still on the proving ground, it was possible to use the two tests: (1) the cytology test (a) to detect uterine cancer, or (b) to detect abnormally high cornification, and (2) to check the thiamine level. It was stated that even in the absence of cancer cells, the demonstration of a linkage of high cornification and low thiamine constituted a possible precancer indication which might be corrected. Since this time, and following a routine cytologic investigation of the cervixes of a large group of several hundred women with no definite gynecologic complaints, cytologic evidence and biopsy

tion in the cervix. If infection does cause a fixation of estrogen in the cervical tissue, the degree of stability of this fixation would also influence excretion levels. It may also help explain the finding of excess tissue estrogens in postmenopausal cancers. If the estrogen is firmly bound in these cells, the blood and urine estrogens might disappear entirely, while that in these tissues might remain. It is uncertain at our present stage of incomplete knowledge how much the concentration of estrogen in cervical tissues may depend upon changes in systemic levels and how much upon local changes. There are two possible considerations. First, the systemic changes which may result from the nutritional deficiency, liver dysfunction, and resultant estrogen accumulation in the blood. On the other hand, the purely local fixation and concentration of estrogen in the infected cervical tissues must be considered. Probably both mechanisms

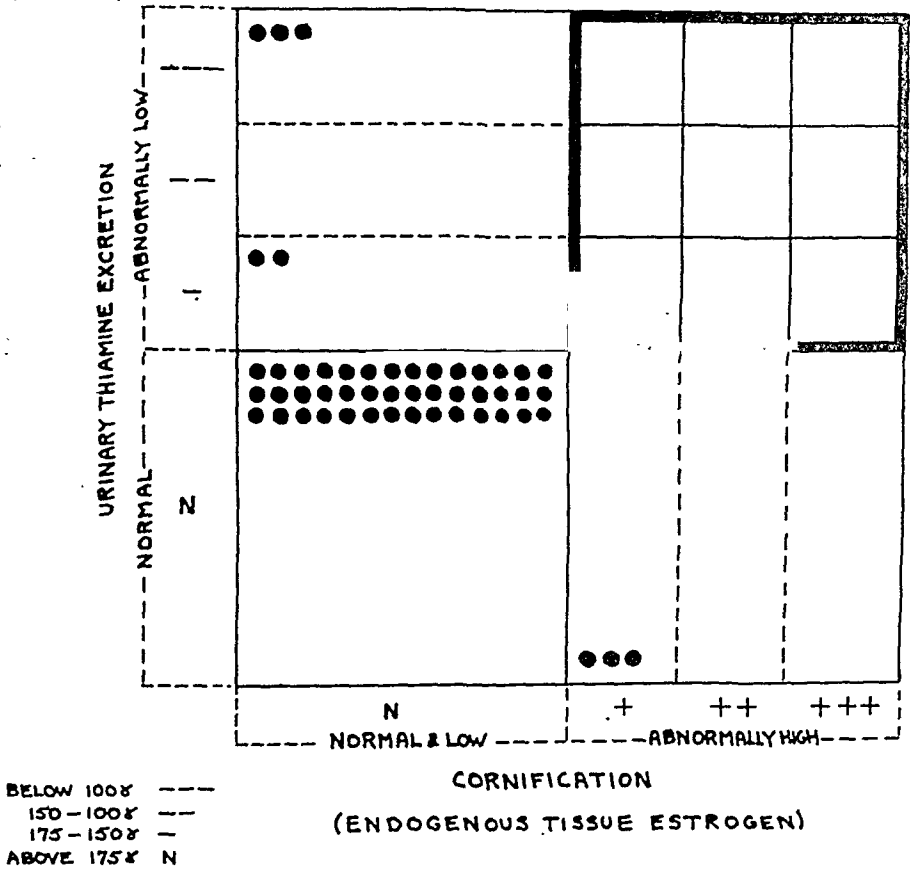


Fig. 12B.—Graphic representation of thiamine-estrogen findings in 50 control cases.

are active, the systemic changes probably varying considerably depending upon the variable dietary intake, the production of estrogen, and its accumulation in the blood. It seems likely that changes in estrogen blood levels might be rapid and considerable. The tissue estrogens in the cervix would also tend to rise with the availability of more estrogen from the blood, but it might not fall as quickly due to the tissue fixation. Such a mechanism would offer at least a partial explanation for the finding of evidence of abnormally high tissue estrogens in postmenopausal or senile women suffering from cervical carcinoma. While the blood may be subject to transient elevations in the estrogen level produced by either a temporary rise in production by the ovary or possibly the adrenal, or by a possible liver block which leads to temporary accumulation of even small traces being produced—such elevations of estrogen though transient might permit the concentration of these estrogens more permanently in the cervical tissue exerting affinity toward this substance.

of blood were noted. These patients have shown in general a low basal metabolic rate of -10 to -20 , while they have exhibited a normal blood picture. In other words, these cases of beginning-cancer show the same evidence of our theoretical carcinogenic mechanism as the more advanced lesions. This fact would seem to be significant because forces in the body controlling growth which become disordered in some specific manner to produce a growth of a



Fig. 14.—Low power of same growth as shown in Fig. 13. Note infected glands and tissues.



Fig. 15.—Clinical appearance of cervix in same case at the present time.

malignant nature—these forces are not necessarily fixed in their intensity and chronicity. Recent comparative studies of rates of growth in a preinvasive as compared to invasive carcinoma of the cervix reveal most interesting and hopeful evidence of two separate rates of growth activity in the preinvasive, silent stage as contrasted with the invasive clinically demonstrable stage. Evidence has been reported elsewhere²⁸ that a long interval of from one to eight years, or longer, may elapse between the preinvasive and the invasive stage of

confirmation have been found of microscopic preinvasive carcinomas in a surprisingly large number of cases. It is of interest, and probably also of significance, that these patients appear clinically to be in good gynecologic health with the exception that they show signs of the so-frequent chronic cervicitis. Yet their squamous cells scraped from the squamocolumnar junction of the cervix³⁵ show evidence of neoplastic changes in addition to abnormally high tissue estrogens. These patients have also shown the same high consistency in their deficient thiamine excretion levels.

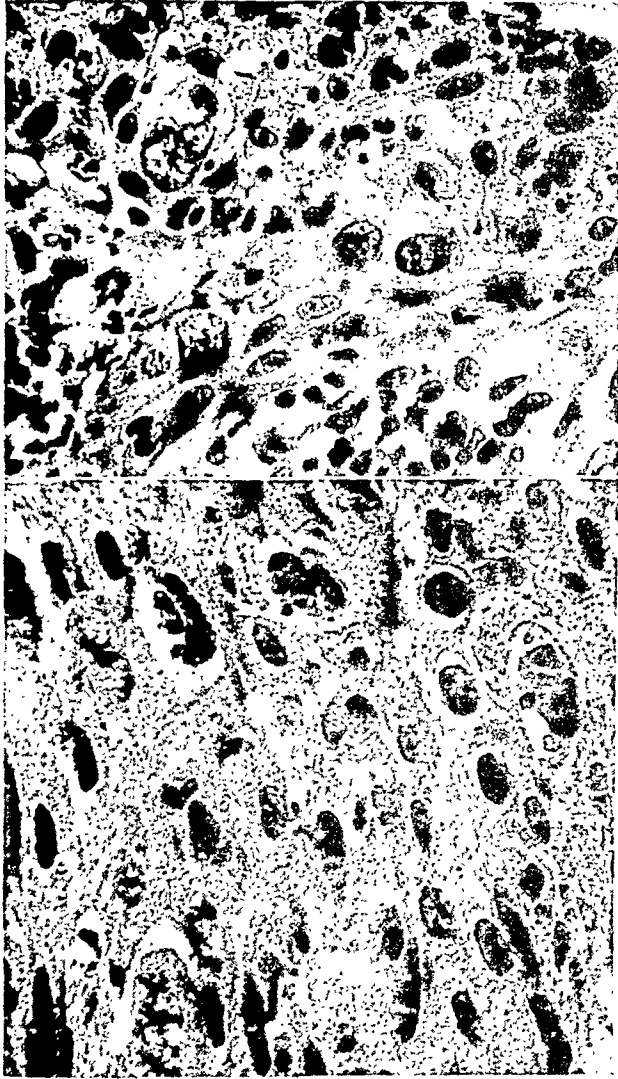


Fig. 13.—Pathologic study of cervical growth under high power. Observe numerous mitotic figures and large malignant-appearing cells. Two different pathologists have diagnosed this growth as carcinoma. Was this cancerlike growth induced in this 25-year-old patient by the administration of estrogen while nutritionally deficient? Inflammatory exudate throughout sub-epithelial tissues (Fig. 14) is apparent.

These cases proved instructive, firstly because they may be considered to be "cancer-in-the-making." The lesions are minute and no secondary influence upon general body nutrition was apparent. Cachexia was totally absent, and any possible reverse toxic action (if any occurs) of a large malignant growth upon the liver and body metabolism was absent. Symptomatically, most of these patients complained of mild gastrointestinal disturbances with loss of appetite and constipation and occasionally some loss of weight. Gynecologically, leucorrhea, menorrhagia, and occasional intermenstrual spotting

It was considered to be of some significance that 18 of 22 of our cancer cases tested showed borderline or abnormal function as indicated by the bromsulphalein or cephalin flocculation tests. While we must consider that liver impairment may result from some toxic substance elaborated by the malignant growth, this would hardly seem to be the explanation in lesions of microscopic size. Of passing interest is the fact that of the cases showing this evidence of impairment, all of them at this time showed deficient thiamine excretion. Following the administration of thiamine chloride orally and parenterally to six of them, definite change in the liver function reading was noted within seven to ten days. The abnormal liver function reading in all six of these cases had changed to a normal reading. No other change in the regimen in these cases could be determined, which might explain this improvement. The clinical improvement in cancer cases, regardless of stage, is striking. Following correction of nutritional defects, these patients lose some of their cachetic appearance and show improvement in appetite. Some of them have, over a period of months, improved dramatically, gaining as much as twenty to thirty pounds in weight. It has been observed, too, that patients receiving thiamine or B complex in large doses during the course of x-ray or radium treatment, have exhibited a greatly reduced degree of the usual radiation sickness. Such clinical changes might be expected in the presence of a deficiency. But the change in the liver function readings may be of some significance. While the small number of cases studied for liver function permit no definite conclusions, the leads established demand more intensive investigation.

Speculation on Nature of Cancer Production

Is squamous cancer of the cervix the disordered growth response to persisting estrogen concentration in inflamed squamous tissues in the presence of a nutritional deficiency? Does a thiamine deficiency act directly upon the proliferating squamous cell, impairing its enzyme pattern and its metabolism?

While the evidence presented of excess tissue estrogens, of chronic persisting infection in the cervix, and of a general deficiency of excretion of thiamine by urinary assay perhaps offers an incomplete picture to provide proof of cancer causation, the correlation of these three factors provides an interesting speculative picture. We might say that in cervical cancer the linkage between chronic infection and estrogen fixation in cervical cells explains a great deal regarding the relationship of inflammation to cancer growth. Many gynecologists have noted the great frequency of occurrence of chronic cervicitis. Probably four out of five cervixes show some low-grade persisting infection in the cervix which probably remains there for years. The fixation and resultant concentration of estrogen in the cervix would tend to produce increased proliferation of the squamous cells which may be continuous over a period of years. The chronic infection has been compared to a factor producing chronic irritation in these tissues. The addition of the estrogen factor further accelerates healing or growth response as a result of this tissue-selective growth stimulant. The associated nutritional deficiency may act entirely through the liver, or its action may be purely local in the individual tissue cells, or there may be a combination. An interesting possibility is the speculation that the continuous estrogen stimulation upon the squamous cells producing chronic proliferation may result in exhaustion of these cells or of the tissue enzymes leading to an aberrant type of growth reaction. The precise relationship of the nutritional deficiency to the "wearing-out" process of the cells leading to the abnormal type of growth is not clear. Its action upon liver function and resultant estrogen accumulation is easily understood. But whether there is a direct action locally in the tissues upon cell

cervical squamous carcinoma. At some point during this interval, a definite change occurs. Whether this is due to a change in force, intensity, or chronicity of the factors under consideration is not certain. Some gynecologists have argued that a change may also occur in the opposite direction, i.e., to produce a regression and spontaneous disappearance of the lesion rather than a progression to clinical carcinoma. While it is fascinating to dwell upon this prospect, evidence to date has revealed numerous cases to show that invasion ultimately does occur, while no evidence has as yet been reported to show that the reverse may happen. This remains as an interesting possibility for further investigation. Whatever particular combination of forces may initiate an invasive cancer, is probably not the same combination of forces which may act to sustain this growth, once fully established. We know that once full-blown, invading carcinoma becomes a reality, it becomes totally independent of all body controls, and from this point onwards it would doubtless continue in its uncontrollable growth habit regardless of a diminution of whatever growth-stimulating factors may have produced it.

Induced Cancer of Cervix?

The administration of an estrogen (stilbestrol) to a 25-year-old patient showing chronic cervicitis and a low thiamine excretion level was followed by the appearance of a cancerlike growth at the squamocolumnar junction (Figs. 13, 14 and 15). This patient complained only of leucorrhea, fatigue, and constipation. The administration of estrogen in moderate doses over an interval of ten weeks was followed by vaginal spotting of blood, and cytology tests revealed cells of malignant morphology. Complete excision of the squamocolumnar circle of the cervix revealed the lesion as shown. Details of this case have been reported elsewhere.³⁹ The appearance of the cervix six months following surgical excision with the electro-cautery is shown in Fig. 15. The cervix appears normal, and no further evidence of disorder is detectable, clinically or cytologically.

Human Liver Function Studies

While most authorities agree that liver function tests in human beings leave much to be desired, some progress has been made by certain investigators toward assessing various functions of the liver on the basis of the available liver function tests. Dr. M. M. Hoffman of the Medical Laboratories of the McGill University Clinic, who has studied liver function tests intensively, states that no single test has as yet been elaborated to assess liver damage, and it is possible to have liver damage sufficient to interfere with estrogen inactivation without this damage being detectable by the tests at present at our disposal. However, some attempt has been made by us to gain what information might be available in this regard in certain of our cancer cases, and whenever our cancer patients were accessible for liver function study certain tests were taken. The results of these are presented in Table II.

TABLE II. LIVER FUNCTION RESULTS—CANCER CASES

| | |
|--|------|
| Number of cases having liver function test | 20 |
| Number of these cases showing low thiamine | 20 |
| Number of cases showing abnormal cephalin flocculation or bromsulphalein readings | 11 |
| Per cent showing abnormal liver function tests | 55% |
| Number of cases having liver tests before and after correction of thiamine deficiency | 6 |
| Number of cases showing correction of abnormal liver reading after thiamine therapy | 6 |
| Per cent showing corrected reading | 100% |

with variations in force, intensity, and chronicity of the particular carcinogenic factors which influence that particular organ. It may be, then, that the blow to the breast which the patient recalls, is of more than coincidental significance. While it may prove harmless in the presence of a normal nutritional and hormonal balance, in the presence of the abnormal metabolic status, the resultant healing growth-reaction may result in growth of a malignant character.

Comment

During the course of this study we have been impressed by the consistent finding of a different cell morphology at the squamocolumnar junction, both in cytology smears and in tissue biopsies, in cases exhibiting the infection-estrogen-nutrition combination. This unusual cell-change has been most impressive in the group of microscopic preinvasive cancers, where no demonstrable clinical growth was detectable. Yet the cell-change was definite in cytology and was consistently confirmed by biopsies (e.g., Figs. 16 and 17).

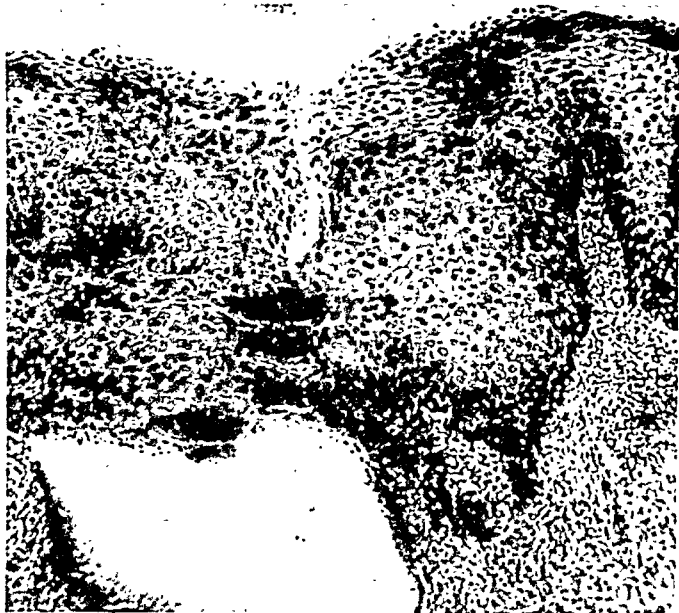


Fig. 17.—Extremely hyperactive proliferation in cervical epithelium in 28-year-old manifesting cervicitis, low thiamine and high tissue estrogens. Note marked nuclear changes in squamocolumnar zone.

We feel sure that cytology techniques offer us a valuable means of early cancer diagnosis. But more significantly they also provide us with new microscopic sights to probe into the hidden recesses which have long held the secret of the fundamental nature of cancer growth.

Summary

1. Cytology studies have been found valuable in early diagnosis of cervical cancer, and in estimating endogenous estrogen.
2. Comparative vaginal and cervical cornification counts have revealed greater concentration of estrogens in the cervix in 87 per cent of cases studied.
3. Some degree of chronic cervicitis is believed to be present in four of five adult cervices.

metabolism influencing the character of cell proliferation and growth is uncertain. But such an action seems highly probable. Thiamine is necessary for normal glycogen metabolism, and glycogen is related to estrogen activity in the cell. It has been stated that thiamine is an essential element to permit normal cell growth. It has been shown that the human carcinoma cells are low in thiamine, and the present studies have confirmed a low thiamine excretion level in a great majority of human cancer cases. This speculative action of the nutritional element would appear to be a specific influence upon growth behavior of the cell rather than a mere acceleration of cell exhaustion which one would anticipate in any growing tissue whose essential nutrition is impaired. Perhaps the exhaustion state represents an end-point in the ability of the cell to proliferate and reproduce a mature differentiated cell-product, under the environmental conditions of stress imposed by an impaired enzymic pattern. Beyond this end-point evolutionary reversion to a more primitive embryonic type of cell-offspring might occur producing the malignant cell.

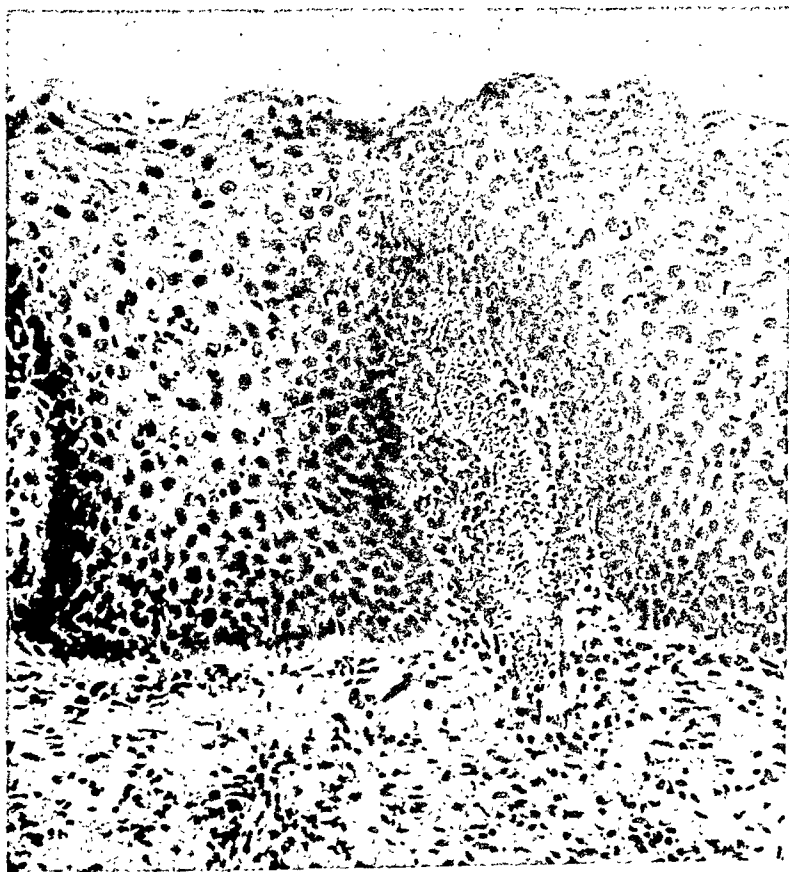


Fig. 16.—Moderately hyperactive proliferation of cervical epithelium in 31-year-old patient manifesting cervicitis, low thiamine, and high tissue estrogens.

May it not be that in all cancers there are two essential combinations of forces? First, a general body metabolic disorder characterized by a nutritional deficiency, possibly liver changes, and resultant hormonal changes. This metabolic disorder may exist with variable intensity and chronicity for years without producing cancer. Ultimately the second factor is added to the picture, namely the focalizing factor of any chronic damaging or irritating condition which provokes growth response. Whether due to infection, or inflammation, or damage, an aberrant type of growth response results, varying in character

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4. Estrogen-fixation and concentration in infected cervical tissues is believed to be a growth-stimulating factor predisposing to cancer.

5. Evidence of excessive tissue estrogen has been found in 92 per cent of 50 cervical cancers.

6. Deficient urinary thiamine excretion has been found in 86 per cent of 50 cervical cancers. Ten per cent of 50 controls showed the same deficiency.

7. Riboflavin deficiency was found in 38.8 per cent of cancer cases, and in 6.8 per cent of the controls.

8. Studies of cervical biopsies illustrating abnormal growth proliferation in the presence of cervicitis, excess tissue estrogens, and low thiamine excretion are presented.

9. Partly by speculation, partly by interpretation of evidence presented, an attempt is made to correlate infection, excessive tissue estrogens, and nutritional deficiency in the production of cervical carcinoma of the squamous type.

10. The possible concentration of estrogen around cervical cancer lesions arouses great hope for improved therapy with radioactive isotopes. Just as thyroid cancer may succumb to radioactivated iodine, so also may the selective affinity of estrogen for proliferating Müllerian tissues enable successful treatment of cancer of the cervix.

Dr. W. A. G. Bauld, Director of the Gynecologic Cancer Clinic, has closely collaborated throughout, and by his keen interest, ready counsel, and constructive criticism has contributed immeasurably to the successful completion of the present stage of this work. Appreciation is also expressed to Drs. J. R. Fraser, N. W. Philpott, and J. S. L. Browne for valuable advice and cooperation in the preparation of this work: to the Nutrition Department of the Medical Laboratories of the McGill University Clinic, and to Dr. P. J. Kearns, Chief of the Gynecologic Pathology Laboratory of the Royal Victoria Hospital: and to Drs. W. A. Andreae and M. M. Hoffman for their assistance and advice regarding nutritional studies and liver function tests, respectively.

Grateful thanks is also tendered to Dean Meakins, Director of the Medical Laboratories of the McGill University Clinic. Assistance in this work has also been rendered by Dr. Paul Chevalier, Molson Fellow in Cancer Research, and Miss Evelyn Dakin, Director of Technicians in the Gynecytology Laboratory, who, through her tireless efforts and technical genius, has made a major contribution to this work. Mrs. Dorothy Peden of the Gynecologic Pathology Department has rendered valuable help in preparing pathologic sections. Miss Janet Alexander has done excellent work in the biochemical studies of the thiamine and riboflavin levels.

Photomicrography by H. S. Haydon, F.R.P.S., and H. Coletta.

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All possible landmarks were utilized to facilitate superimposition of photograph and roentgenogram. Actually, they could not be matched exactly because of dispersion of roentgen rays. In other words, it is impossible to superimpose two pictures when one is made with parallel light rays and the other with roentgen rays diverging at angles approaching 35 degrees. Many methods, including the metal markers mentioned above, were tried and discarded. The best possible correlation of roentgenogram and photograph was achieved by trial and error, after careful study of all discernible landmarks. Three observers in joint session, including Mr. Fred Kent, official photographer of the University of Iowa, carefully matched each pair of pictures. The resulting product was legible by transmitted light, but unsuited for reproduction on the printed page. Therefore, the accompanying diagrams were carefully drawn from the roentgenograms and photographs and faithfully adhere to the original. In each instance red lines indicate the supine, or the lateral recumbent position, as the case may be. Solid black lines represent the sitting position. Standing is portrayed by dotted lines.

For purposes of this study, four variations of uterine position are recognized, viz: station, flexion, version, and cession. "Station" is employed to indicate the height of the cervix in the pelvic basin. "Flexion" refers to bending of the uterine canal. "Version" means rotation of the entire uterus around a transverse axis. The amount of "cession" indicates the distance of the cervix from the symphysis pubis. Thus, a "retroceded" uterus sags posteriorly toward the sacrum.

Results

The original study, presented as an exhibit and referred to above, included thirteen patients of whom ten were normal from a gynecologic standpoint, and three suffered with genital prolapse. Since results were quite uniform in these women, irrespective of parity, it is superfluous to diagram the findings of each. Therefore, only average results illustrated by a normal subject with habitual anteversion (Fig. 1), a normal subject with habitual flexioretroversion (Fig. 2), and the findings from a patient with incomplete (Fig. 3), and a patient with complete prolapse (Fig. 4) are presented.

Habitual Anteversion.—Figs. 1A and 1B represent characteristic positions of the uterus in a subject with normal genitalia and habitual anteversion. The results portrayed here are typical, irrespective of parity, of other women of the original study. As might be expected, lowest uterine stations accompanied vertical positions of the trunk (Fig. 1A and 1B). There was no significant alteration of uterine flexion or version with change of body posture. On the other hand, retrocession was perceptible in the standing posture, and markedly increased with sitting.

Habitual Flexioretroversion.—Figs. 2A and 2B represent characteristic positions of the uterus in a subject with normal genitalia and habitual flexioretroversion. The results portrayed here are typical, irrespective of parity, of other women of the original study. In conformity to the previously described subject, the lowest stations accompanied vertical positions of the trunk. There was little change in flexion and version between the lateral recumbent and standing postures. On the other hand, a considerable increase in retroflexion and retroversion was noticed when the subject sat upright. The amount of retrocession in the two erect attitudes (sitting, standing) was similar, but much greater than with right lateral recumbency.

Incomplete Prolapse with cystocele.—Figs. 3A and 3B demonstrate uteropelvic relationships in a postmenopausal woman with incomplete prolapse and moderate cystocele. Flexion did not occur with any position. Interestingly,

THE EFFECT OF BODY POSTURE ON UTERINE POSITION

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FORTY-FIVE years ago Tandler¹ taught that the normal uterus is a movable organ. In 1936, Harris, Mengert, and Plass² demonstrated with bimanual palpation that it alters its position in response to postural change. Diddle, Mengert, and Earl³ confirmed this finding radiographically in 1939 with an exhibit of superimposed photographs and roentgenograms. Part of this material was utilized in the present study to illustrate the amount of uterine movement with change in body posture. Diagrammatic line drawings were used, since it was impossible from a practical standpoint to reproduce the original material.

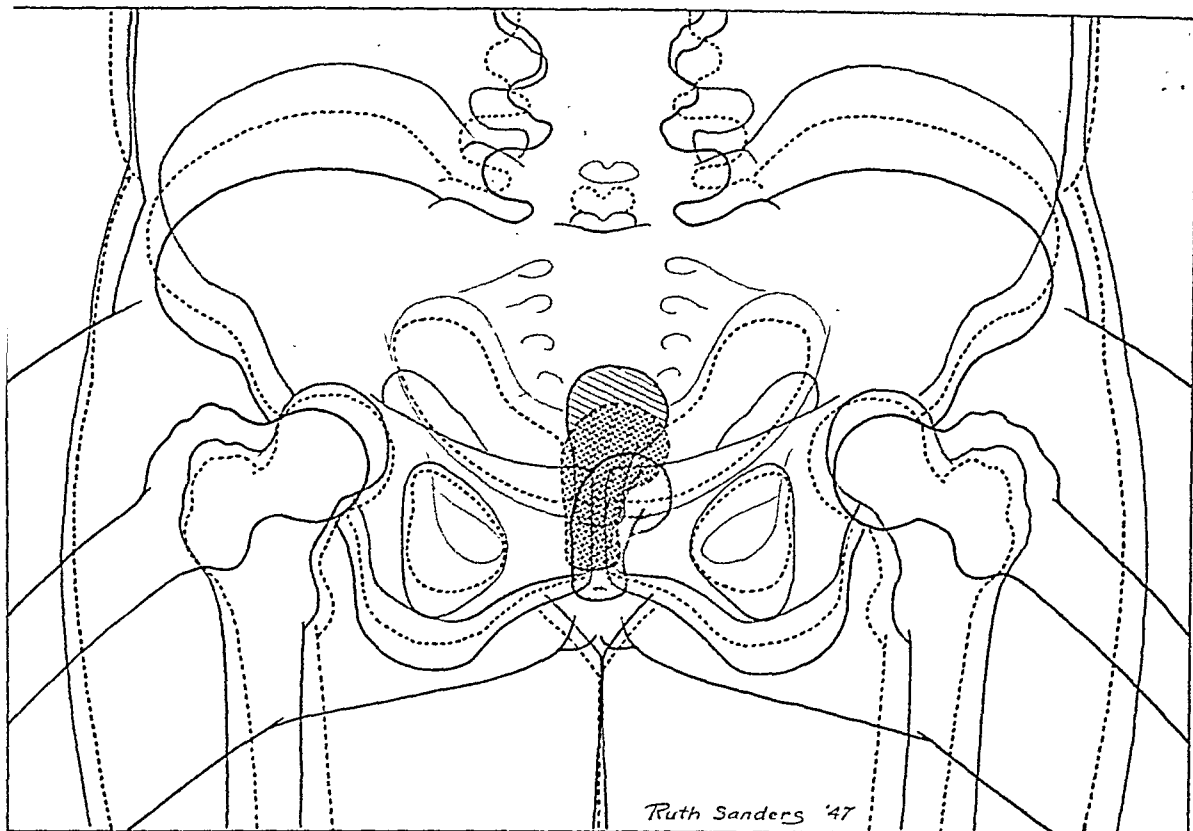
Subjects

Data of four representative subjects were selected from the thirteen gynecologic patients forming the basis of the exhibit by Diddle, Mengert, and Earl.³ Two of these four subjects were normal, apparently healthy, young women admitted for various minor complaints not stemming from the pelvis. They were selected because one of them presented typically average genitalia, while the freely movable uterus of the other habitually lay in mild flexioretroversion. Two were postmenopausal, and were admitted for repair of an incomplete and a complete uterine prolapse, respectively. All four women were in excellent nutritional states.

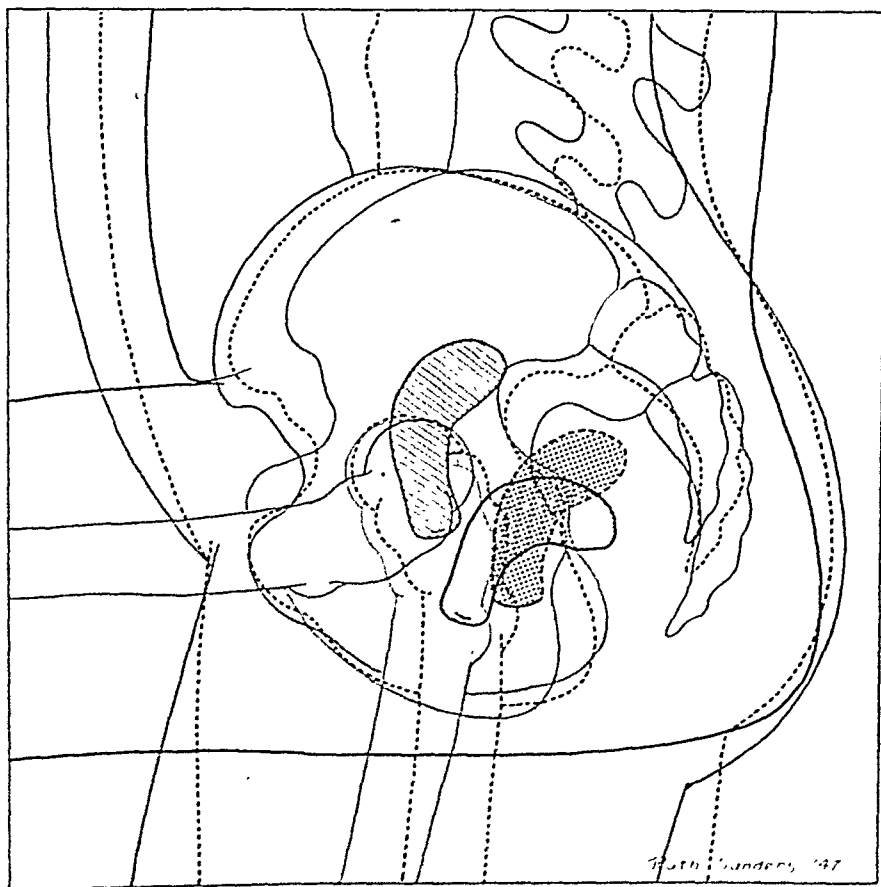
Method

The length and direction of the uterine canal were visualized by means of a ureteral catheter, inserted to the fundus, and cut off flush with the external cervical os. The surface of the vaginal portion of the cervix was visualized with a snugly fitting, aluminum contraceptive cap. The total weight of both of these artifacts was small, less than 13 Gm., and is believed to exert no significant influence on the final result. In addition, the urinary bladder was delineated in two subjects (normal anteversion and complete uterine prolapse) by the instillation of sodium iodide solution. Metal markers were placed on the medial and lateral aspects of the right thigh and, in some instances, above the right iliac crest.

Anteroposterior roentgenograms of each subject lying supine were made. Following this she turned to the right side for the lateral recumbent view. Next, anteroposterior, and right lateral roentgenograms were made with each subject successively sitting and standing. The subject remained in a given position for fifteen minutes preceding exposure of each film to allow for visceral accommodation and adjustment, possibly an unnecessary precaution. Photographs of the nude subject in the several positions were made from a standard distance.



A.

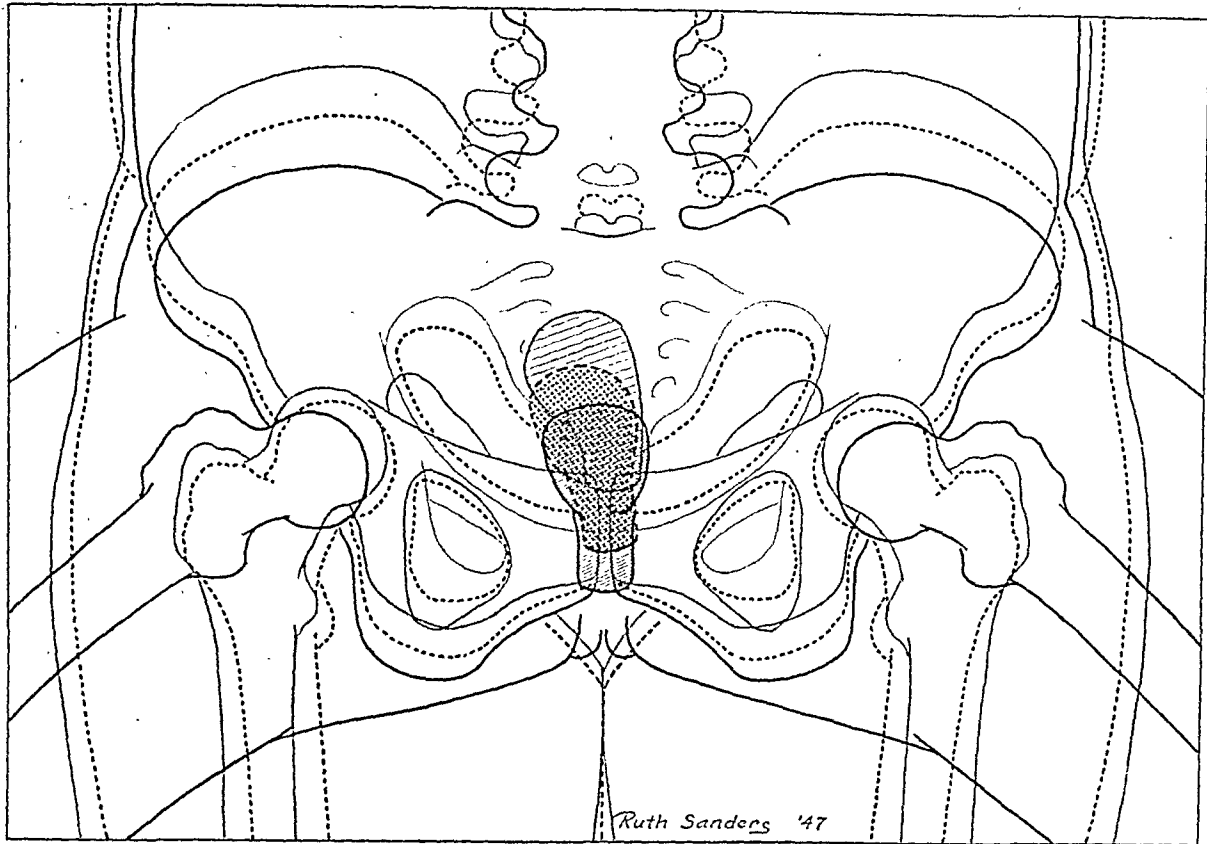


B.

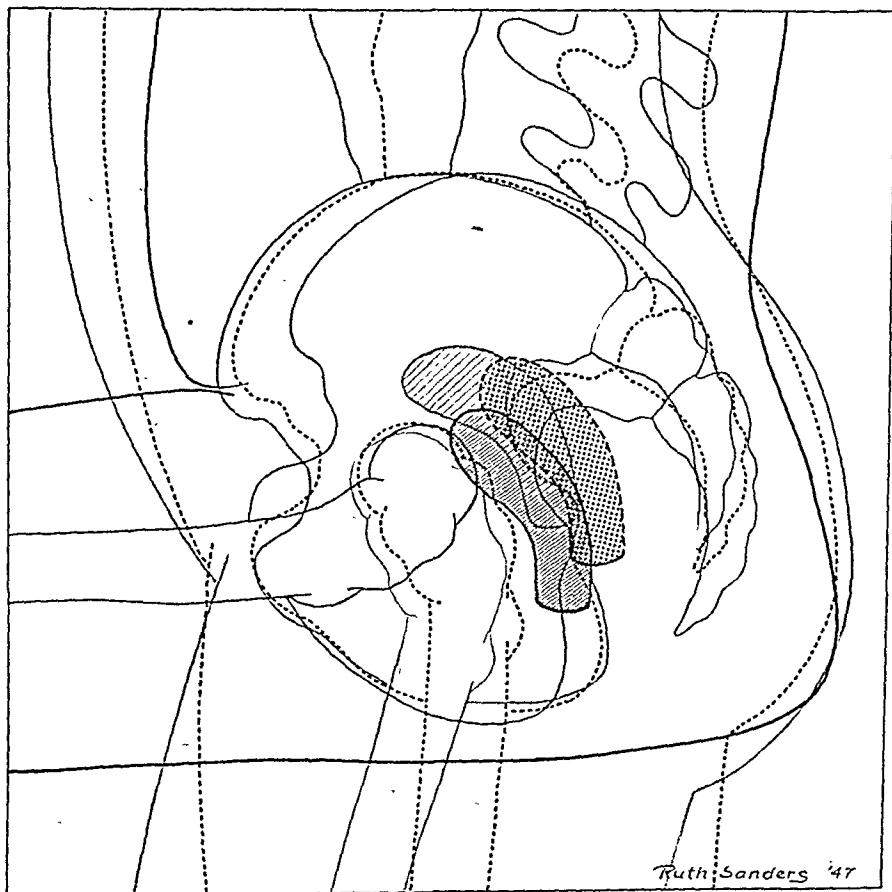
Fig. 2.—Habitual flexioretroversion.

Fig. 2A.—Note slight, descending station of the uterus. The uterus reached its lowest station with the patient sitting.

Fig. 2B.—Retroflexion and retroversion were noticeably increased in the sitting posture. Retrocession was increased with both erect attitudes (sitting, standing).



A.

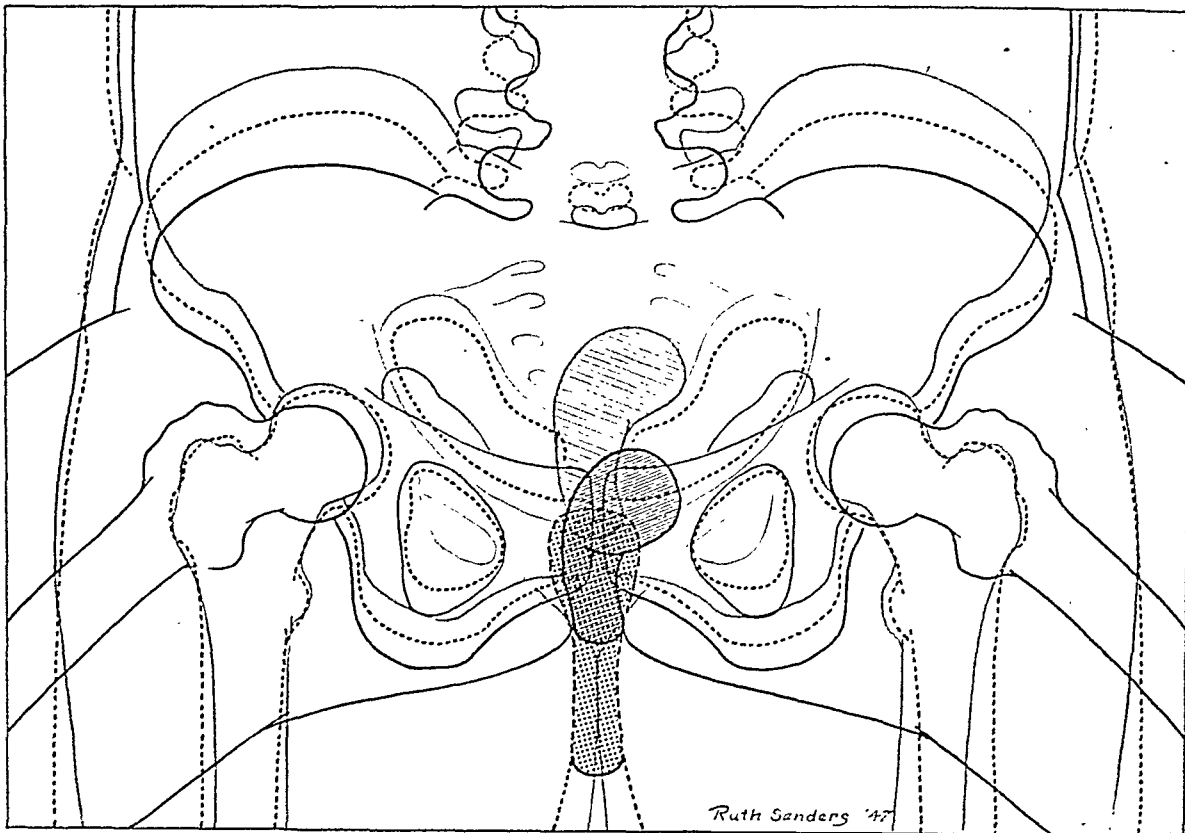


B.

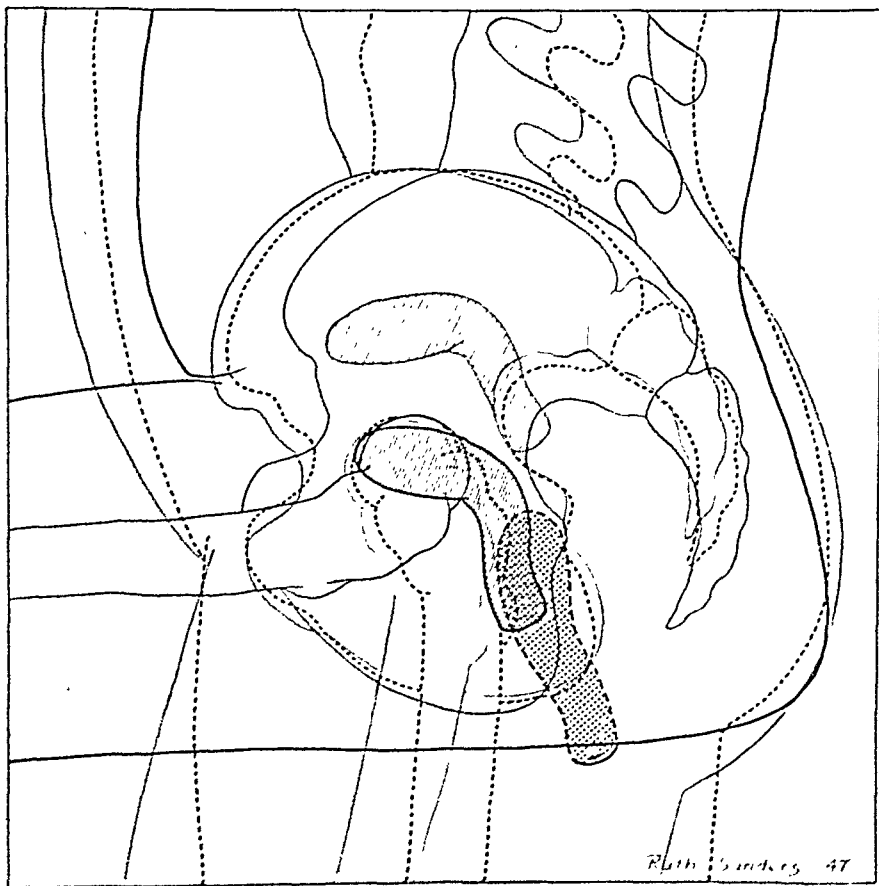
Fig. 1.—Habitual anteversion. Red lines indicate conditions when supine; solid black lines, sitting; dotted lines, standing. This sequence is observed in Figs. 1, 2, 3, and 4.

Fig. 1A.—Note lowest uterine stations accompanied vertical positions of the trunk.

Fig. 1B.—Descent of the uterus is also evident in this view. Note definite retrocession in the sitting posture.



A.

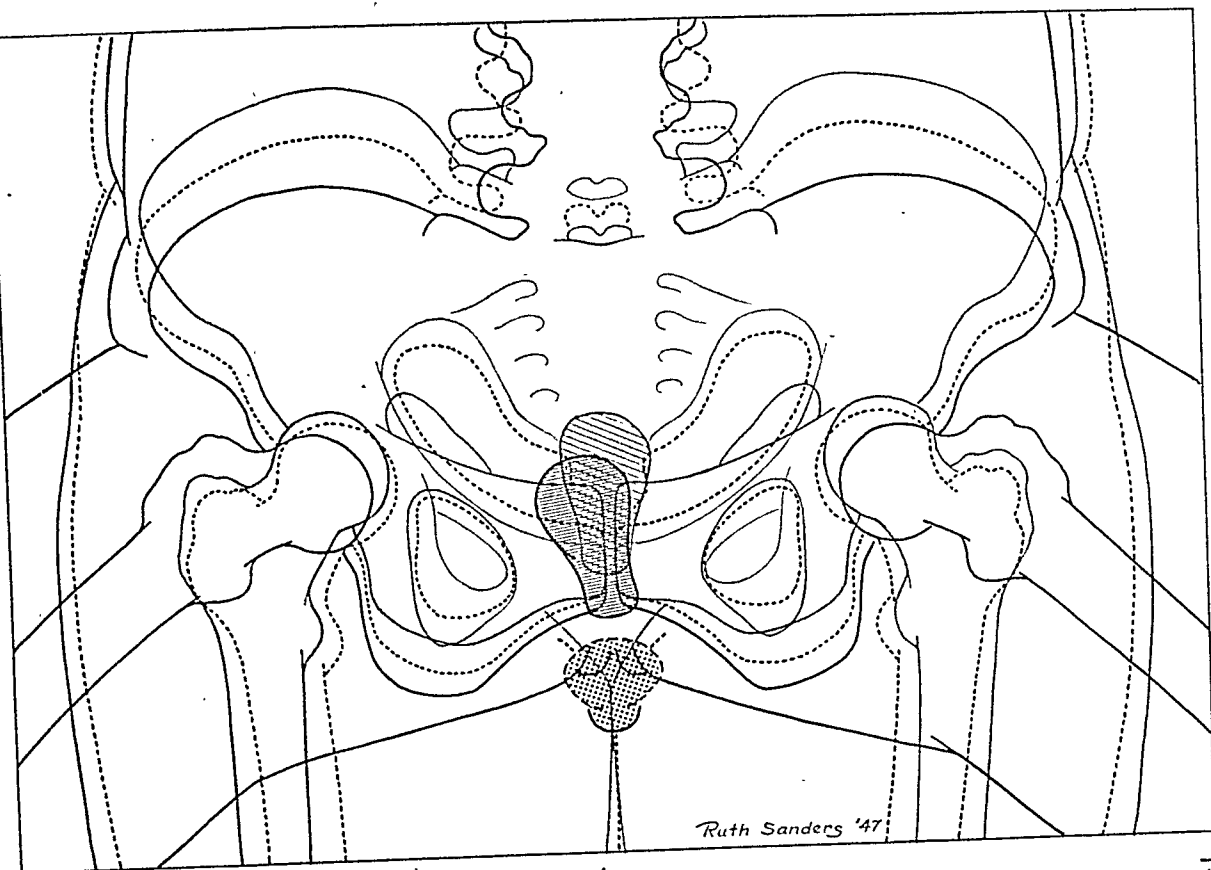


B.

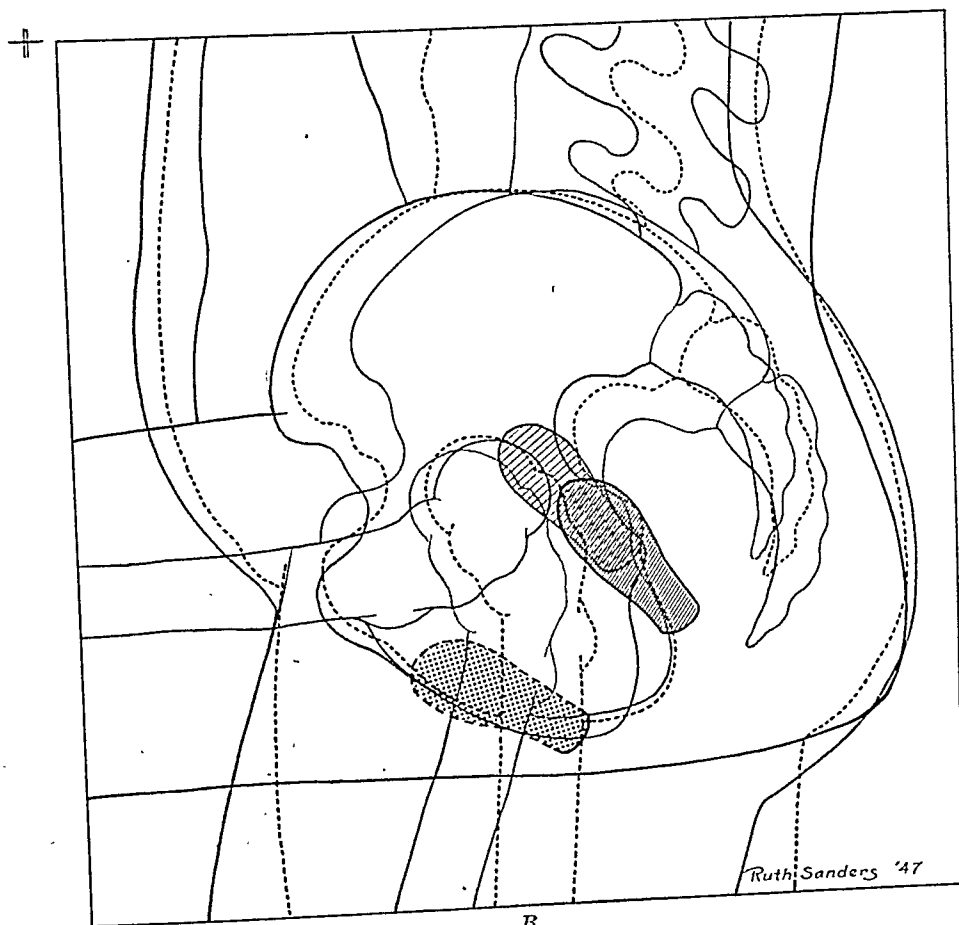
Fig. 4.—Complete prolapse.

Fig. 4A.—Note apparent elongation of cervix as the uterus descended. (Complete prolapse did not happen to occur during the course of the study.)

Fig. 4B.—Note elongation of cervix and straightening of the uterine canal with descent.



A.



B.

Fig. 3.—Incomplete prolapse with cystocele.

Fig. 3A.—Note descent of the uterus as the patient became progressively erect.

Fig. 3B.—Note increased anteversion with marked forward displacement of the entire uterus (*anteversion*) in the standing position. Also note the uterine canal was nearly horizontal. These findings are direct negation of the common teaching that *retroversion* is a necessary prelude to prolapse.

version was *forward*, and was especially marked in the standing posture. Coincident with increased anteversion in standing, the *entire uterus descended*, and lay at the vulval orifice with the axis practically horizontal. This finding is a direct negation of the common teaching that *retroversion* is a necessary prelude to uterine prolapse.

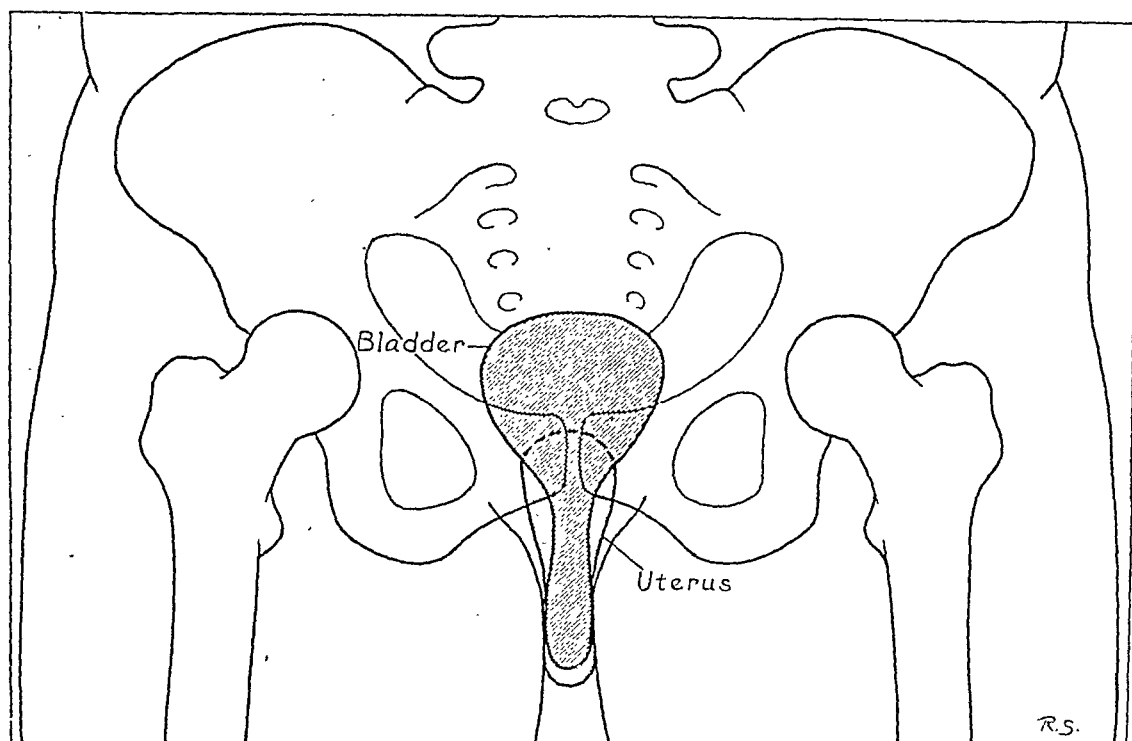
Complete Prolapse.—Figs. 4A and 4B illustrate conditions in a post-menopausal woman with complete prolapse, defined as descent of the entire uterus outside the carunculae myrtiliformis. Such conditions were found in this patient at the times of admission and operation, but not during the course of this study. A few days' bed rest frequently permits an amazing amount of recovery of the supportive powers of the fascia propria. On the other hand, the full extent of the prolapse promptly recurs after resumption of the erect posture. Uterine station was essentially normal with the patient supine and, as might be expected, the lowest station accompanied the standing position. Flexion, most marked with the patient lying on her right side, diminished when she sat and disappeared when she stood erect. This is perfect correspondence to the classic teaching that the anteflexed uterus cannot prolapse. It is of interest that straightening of the uterine canal accounts for its apparent lengthening in the anteroposterior view (Fig. 4A). Version and cession were not significantly altered by change of posture.

The Urinary Bladder.—Figs. 5A and 5B show the relationship of the urinary bladder to the prolapsed (Fig. 5A) and the normally placed (Fig. 5B) uterus. The subjects of Figs. 4 and 1, respectively, were used for this demonstration. As mentioned earlier, the urinary bladder was rendered opaque to the roentgen ray and is illustrated by solid, slanting lines. The uterus is delineated by dotted shading. The bladder assumed a gourdlike shape in the patient with prolapse (Fig. 5A), and its floor descended outside the body with the cervix. Moreover, the bulk of the urinary bladder occupied a station above that of the uterine fundus. In other words, the uterus lay posterior, instead of superior, to the urinary bladder. Obviously the saclike, dependent portion of the bladder cannot be emptied completely, and accounts for the residual urine commonly seen with this condition. Fig. 5B of the normally placed urinary bladder of the subject of Fig. 1 is inserted for comparison.

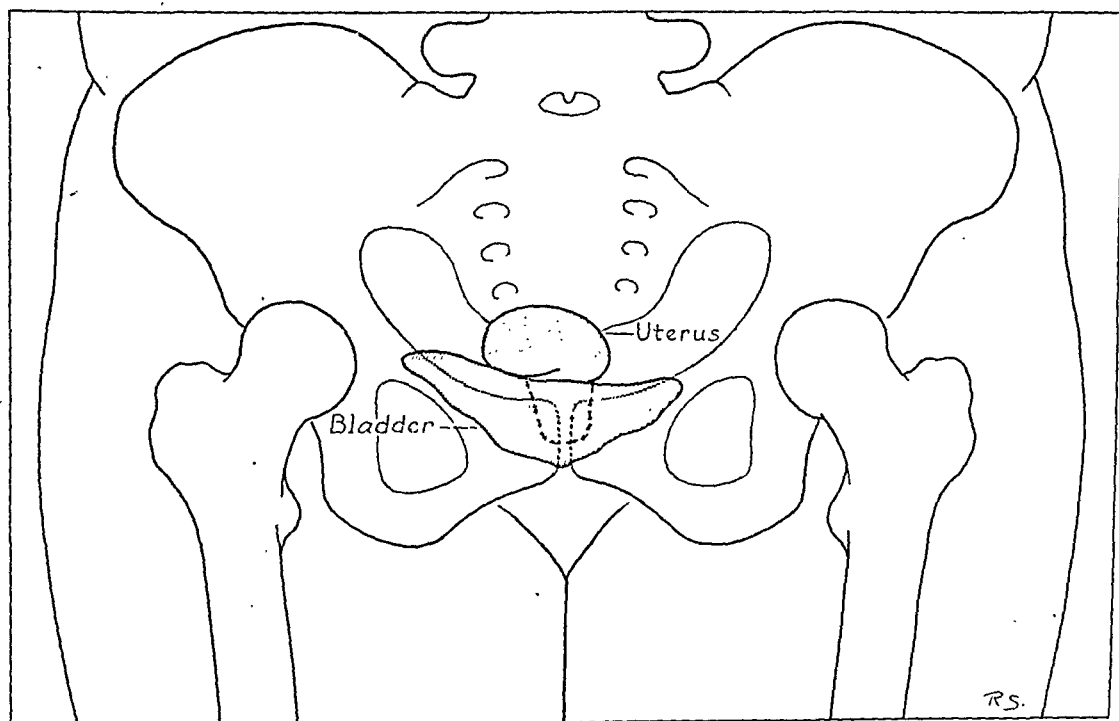
Discussion

Objectivity is the chief value of the present study. Movement of the uterus, with the canal artificially rendered opaque by lightweight materials, was seen and measured on roentgenograms. Harris, Mengert, and Plass reported uterine movement from ante- to retroversion with change of body posture of women confined to bed with pulmonary tuberculosis but their study was based upon the subjective interpretation of bimanual palpation. Gross change only was reported and they found that version from anterior to posterior uterine position (or vice versa) did not occur in less than twenty-four hours.

Passage of time is important in any consideration of uterine mobility, since intestines must be displaced before *profound* change is possible. Moreover, uterine weight, effective for intestinal displacement, is small in relation to that of viscera displaced. Therefore, the rate of change is slow and depends to some degree upon intestinal peristalsis. On the other hand, minor degrees of change can occur during the passage of minutes, without the necessity for in-



A.



B.

Fig. 5.—Urinary bladder relationships. Only one posture, standing, is depicted here. Therefore, the linear system pertaining to Figs. 1, 2, 3, and 4 is not applicable. Solid, slanting lines represent the urinary bladder. Dotted lines indicate the uterus.

Fig. 5A.—Visualized urinary bladder of patient with complete prolapse (Fig. 4). Note position of the uterus in relation to the floor and dome of the bladder, with its dependent sac preventing complete emptying.

Fig. 5B.—Visualized urinary bladder of patient with habitual anteversion (Fig. 1) inserted for comparison.

STUDIES IN RH-ISOIMMUNIZATION IN PREGNANCY

Observations in a Series of Ninety-Six Sensitized Women

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CONTRIBUTIONS to medical literature relating to the Rh factor have reached an impressive total since the discovery of this erythrocytic antigen by Landsteiner and Wiener.¹ As a result of these studies many fundamental facts concerning the clinical, genetic, immunologic, anthropologic, and pathologic aspects of the subject have been elucidated. Students in this field, however, continue to be aware of the existence of many unsolved problems. A striking lack has been the application, in a comprehensive manner, of this mass of knowledge to large groups of pregnant women and their offspring. Data accumulated from such material would serve not only to lend numerical support to pre-existing ideas, but would also tend to clarify certain still-nebulous facets of the subject. It is the purpose of this paper to deal with observations made on a group of 12,275 patients studied during the period August 1, 1945, to August 31, 1946. Of the total, 96 isoimmunized women were encountered. Particular reference will be made in the latter group to a correlative study of quantitative prepartum antibody titer with neonatal mortality.

Even as late as 1945 Rh studies were, in general, being done in a sporadic fashion. The birth of an obviously erythroblastotic infant or an obstetric history suggestive of this complication were the usual indications for serologic studies. In an effort to correct this situation in the community, the Obstetrical and Gynecological section of the Baltimore City Medical Society in August, 1945, sponsored the establishment of a central laboratory, the purpose of which was to make readily available to every physician facilities for Rh studies on all expectant mothers. The organization and method of operation of this laboratory have been fully described in a previous publication.² Owing to the splendid cooperation of physicians and patients, it has been possible to make systematic studies in the large group of patients referred to above.

In succeeding pages the following topics will be discussed:

- I. Distribution and Incidence of Rh Types.
- II. Distribution and Incidence of Rh-Isoimmunization.
- III. Incidence of Erythroblastosis Fetalis.
- IV. Nature and Specificity of Antibodies.
- V. Correlation of Prepartum Antibody Titer With Neonatal Mortality.
- VI. The Course of Isoimmunization During Pregnancy and in the Puerperium.
- VII. Postpartum Persistence of Antibodies.
- VIII. Correlation of Parity With Initial Evidence of Rh-Isoimmunization.

testinal displacement. It is entirely probable that the gross changes reported by Harris, Mengert, and Plass require hours because of the necessity of intestinal displacement. The minor changes demonstrated by the present study may be effected immediately because intestines are locally compressed and not displaced.

It is commonly taught that the anteverted uterus cannot prolapse. In other words, the uterus must assume midposition or become retroverted before descent begins. This was not the case in the patient with incomplete prolapse, since descent occurred with the uterus anteverted, and the canal practically horizontal as she stood erect. Moreover, complete prolapse of the anteverted uterus following the Watkins-Wertheim interposition operation does occur. Such a patient was observed by the authors.

It is apparent that maintenance of uterine station and cession depends upon integrity of fascial support. In contradistinction, the uterine body bends (flexion) and turns (version) on a transverse axis as a result of the combined influences of its muscular tone, position of the intestines, body posture, and perhaps the tilt of the pelvis. It was clearly demonstrated that the normal uterus tended to gravitate in conformity to the several positions assumed by the subject. This tendency was distinctly evident in the normal, and greatly exaggerated in patients with uterine prolapse.

References

1. Halban, J. and Tandler, J.: *Anatomie und Aetiologie der Genitalprolapse beim Weibe* Wilhelm Braumüller, Wien u. Leipzig, 1907.
2. Harris, L. J., Mengert, W. F., and Plass, E. D.: *AM. J. OBST. & GYNEC.* 31: 1009-1012, 1936.
3. Diddle, A. W., Mengert, W. F., and Earl, D. M.: *J.A.M.A.* 112: 1493, 1939.

studies are done on all Rh₁ positive husbands of sensitized women.¹⁰ In many instances the husband's parents are studied in a further effort to determine homo- and heterozygosity.

Whenever possible it has been our policy to study Rh negative patients at monthly intervals up to the eighth month of pregnancy and then at biweekly intervals to term. A sample of cord blood is obtained from the baby at the time of delivery for Rh typing and detection of adsorbed antibodies. Samples of maternal blood are studied on the tenth day and at six weeks post partum. In a limited number of sensitized patients bimonthly serum studies are being made during the first postpartum year to determine the rate of disappearance of antibodies. In all instances where erythroblastosis fetalis occurs in the infant, abstracts of the hospital chart including clinical notes, laboratory data, and pathologic studies become a part of the record.

During the thirteen-month period covered by this study it has been necessary at intervals to alter the protocol because of more recent developments. Although all serologic studies were performed in this laboratory, it should be noted that clinical and pathologic data were assembled from a number of sources. As a result the data in some instances were not as complete as would have been desirable. More recently an effort has been made to establish a uniform procedure for the study of all Rh-negative women and their offspring.

I. Distribution and Incidence of Rh Types

A total of 12,275 women were typed in this laboratory during the thirteen-month period covered by the study. Of this group, 12,140 were unselected individuals whose bloods were examined as a routine of prenatal care. The remaining 135 represent a group referred, because of known Rh negativity, for detailed serum studies. The ratios of positive and negative, white and Negro females conform closely to previously established figures^{1, 4, 11} (Table I). The relative scarcity and expense of sera of anti-Rh' and anti-Rh'' specificity permitted only limited use of these reagents. More recently, all Rh-negative women, their husbands, children, and living grandparents have been studied with all available Rh sera. The continuing availability of large numbers of patients for serologic studies affords opportunity for future genetic and anthropologic investigations.

TABLE I. DISTRIBUTION AND INCIDENCE OF RH TYPES IN TOTAL FEMALE GROUP*

| TOTAL FEMALE PATIENTS | RH POSITIVE | | PER CENT RH POSITIVE | | RH NEGATIVE | | PER CENT RH NEGATIVE | |
|-----------------------------|-------------|-------|-------------------------|-------|-------------|-------|-------------------------|-------|
| | WHITE | NEGRO | WHITE | NEGRO | WHITE | NEGRO | WHITE | NEGRO |
| 12,140 | 7,700 | 2,800 | 84.4% | 92.7% | 1,420 | 220 | 15.6% | 7.3% |

*This is an unselected group and does not include 135 additional known Rh-negative women who were referred here for serum studies.

II. Distribution and Incidence of Rh-Isoimmunization

It has been estimated statistically that in the general population 41 per cent are homozygous or RhRh; 46 per cent are heterozygous, or Rhrh; and 13 per cent are negative, or rhrh. Thus, 11.3 per cent of all matings occur between Rh-negative females and Rh positive-males. As 5.33 per cent (13 per cent of 41 per cent) will be with homozygous men, and 5.98 per cent (13 per cent of 46 per cent) will be with heterozygous men, 5.33 per cent plus one-half of 5.98 per cent, or 8.32 per cent, of all children born will be Rh-positive children of Rh-negative mothers.¹² Theoretically, therefore, opportunity for maternal isoimmunization exists in 8.32 per cent (1 in 12) of all births. However, the observed incidence is somewhat less than one-tenth of the theoretical figure.

Materials and Methods

On all patients referred for study a complete obstetric and transfusion history is obtained. Samples of blood procured by venipuncture are first grouped by Landsteiner's technique.³ The Rh type is determined by the Landsteiner-Wiener⁴ procedure using a suitable dilution of a potent anti-Rh₀ serum of human origin prepared in this laboratory. All definitely positive reactors are thus screened out. No further study is made of these patients unless a previous history of erythroblastosis fetalis is present. In the latter instance Rh', Rh'', Hr and M-N studies are carried out on the patient and her immediate family. All doubtful and negative reactions are checked, using two additional potent anti-Rh₀ sera of human origin obtained from other sources. It is obvious that even with such checking the relatively small proportion (about 1.5 per cent) of positive individuals of types Rh', Rh'', and Rh'R'' will be classified as Rh negative. For all practical purposes such individuals should be classified as Rh negative in regard to isoimmunization by pregnancy or multiple transfusions. In the event that sensitization is detected, negative individuals are further tested with anti-Rh' and anti-Rh'' sera of human origin.*

The detection of Rh-isoimmunization is accomplished by the use of the conglutination test of Wiener.⁵ Further comments concerning certain aspects of this test are made in section V. The so-called "blocking" test⁶ is utilized to afford additional confirmatory evidence of sensitization. This procedure occasionally has been found to offer some technical interpretive difficulties; moreover, it does not lend itself as readily to quantitation as does the conglutination procedure. The Diamond slide test⁷ is occasionally used for a similar purpose. This technique has not been found adaptable to testing on a large scale and, moreover, leads to interpretive difficulties at times due to excessive rouleaux formation and rapid drying of the preparation.

Quantitative estimation of antibodies is carried out by parallel conglutination and agglutination tests upon all sera demonstrating the presence of immune bodies. For this purpose, 2 per cent suspensions of pooled O Rh-positive cells in pooled compatible plasma, serum, and normal saline solution, respectively, are used. More recently, bovine albumin solution as recommended by Diamond and Denton⁸ has been used as the suspending vehicle for the Rh-positive test cells. Parallel studies utilizing a variety of vehicles are being carried on at present. Preliminary studies appear to indicate a greater sensitivity of the procedure utilizing bovine albumin solution. The urgent need for further standardization of the conglutination test is commented upon in a subsequent section of this paper. The conglutination test is controlled by the use of O Rh-negative cell suspensions. In this manner occasional instances of maternal isoimmunization not attributable to the Rh factor may be detected.

The nature of antibodies present in a particular case is determined from the results of the agglutination and conglutination tests. When both procedures give equal titers only bivalent (agglutinins) antibodies are assumed to be present.⁹ A positive reaction with the conglutination test alone is presumed to indicate the presence of only univalent (glutinins) antibodies. Positive reactions of varying titer obtained with both procedures have been taken to indicate the presence of both types of antibodies, when there exists a relative excess of one type. Specificity of antibodies is determined by study of serum reactions with cells of known type including Rh₀, Rh', and Rh'', M and N.

Blood group studies are made of the husbands of all Rh-negative women, and whenever sensitization exists, similar study is made of all living children. Hr

*Sera obtained from the laboratory of Dr. A. S. Wiener.

ingly large group, 26, or 32.9 per cent, gave birth to offspring who displayed no evidence of congenital hemolytic disease (Table III). *This fact, namely, that isoimmunization is not necessarily synonymous with the occurrence of disease in the newborn infant, is worthy of stress.* It has been noted previously¹⁴⁻¹⁶ in a relatively small number of patients.

TABLE III. INCIDENCE OF ERYTHROBLASTOSIS FETALIS IN THE OFFSPRING OF SEVENTY-NINE SENSITIZED WOMEN

| | NUMBER OF INFANTS | PERCENTAGE OF TOTAL |
|---------------------------------------|-------------------|---------------------|
| Evidence of erythroblastosis fetal | 53 | 67.1% |
| No evidence of erythroblastosis fetal | 26 | 32.9% |
| Total | 79 | 100.0% |

On the basis of a 67 per cent incidence of erythroblastosis fetal in 79 patients, approximately four of the seven undelivered patients would be expected to give birth to infants with stigmas of this disease. Thus, in 12,275 deliveries, congenital hemolytic disease occurred 57 times, or once in 215 deliveries for an incidence of 0.46 per cent. In regard to the Rh-negative group (1,775 patients) the incidence of erythroblastosis fetal was 3.21 per cent. This is significantly less than the 4.84 per cent incidence of isoimmunization noted above. Review of our material indicates that the difference is due (1) to failure of maternal antibody titer to reach a degree sufficient to produce disease in the infant, or (2) delivery of an Rh-negative infant in a mother whose antibodies were formed as a result of some previous stimulation.

IV. Nature and Specificity of Antibodies

There is general agreement that antibodies of Rh₀ specificity are those most commonly encountered in cases of Rh-isoimmunization. The ubiquity of the Rh₀ antigen¹⁷ occurring as it does in about 85 per cent of all Rh-positive Caucasians accounts in part for this predominance. The greater antigenic potency of the Rh₀ factor¹⁸ is likewise of importance. Thirty-two of 38 sensitized patients in our series in whom antibody specificity was determined displayed immune bodies of the anti-Rh₀ type (Table IV). Four had Rh₁ antibodies; one, anti-Rh₂; and one, anti-Hr₁ immune bodies. Antibodies of pure Rh' and Rh'' specificity were not encountered. These occur uncommonly and when present are often not in pure form. Thus, sera apparently of anti-Rh' or anti-Rh'' specificity have frequently been found to be mixtures of univalent anti-Rh₀ immune bodies and Rh' or Rh'' agglutinins.¹⁹

TABLE IV. ANTIBODY SPECIFICITY IN THIRTY-EIGHT ISOIMMUNIZED WOMEN

| SPECIFICITY | NUMBER OF CASES | PERCENTAGE |
|----------------------|-----------------|------------|
| Anti-Rh ₀ | 32 | 84.2% |
| Anti-Rh ₁ | 4 | 10.5% |
| Anti-Rh ₂ | 1 | 2.6% |
| Anti-Hr ₁ | 1 | 2.6% |
| Total | 38 | 99.9% |

In our series of cases there were no instances of erythroblastosis due to A-B-O incompatibility. Mass serum studies have resulted in the occasional detection of anti-O immune bodies, usually in low titer. None of these have resulted in clinical disease of the newborn infant. Further details are to be presented in a subsequent publication.

Until 1944 exact studies of Rh-iso-immunization were hampered by the disturbing fact that more than half of the Rh-negative women who gave birth to

In our group of 12,275 pregnant women, 0.77 per cent, or 1 in 128 deliveries occurred in a sensitized woman. That this does not correspond with the actual incidence of erythroblastosis fetalis is noted and discussed in a subsequent section. Of the total, 1,775 were Rh negative. One hundred forty of these women had Rh-negative husbands. Eighty-six Rh-negative sensitized women were encountered in the period comprising this study. In terms of the total negative group, therefore, the incidence of isoimmunization was 4.84 per cent. If the Rh-negative women with Rh-negative husbands are excluded, the incidence of isoimmunization rises to 5.26 per cent.

Among the 1,635 Rh-negative women with Rh-positive husbands, 727 were primigravidas, and 908 multigravidas. There were nine sensitized Rh-negative primigravidas, or an incidence of 1.24 per cent; and 77 multigravidas, an incidence of 8.48 per cent. An almost eightfold incidence of isoimmunization was thus observed in the latter group as compared with the former.

The discrepancy between theoretical potentiality for isoimmunization and its actual occurrence can be attributed to: (1) the relatively infrequent appearance in primigravidas as shown above, and (2) individual variations in placental permeability, antigenic strength, and response to antigenic stimulation.

It is of interest to note that ten instances of Rh-isoimmunization occurred in the group of 10,500 Rh-positive women (Table II). Nine of these occurred in women who belonged to subtypes Rh' or Rh". Since these groups theoretically constitute about 1.5 per cent of the total positive group, the incidence of isoimmunization, 5.7 per cent, roughly approximates that observed in the pure negative group. These observations serve to emphasize the statement previously made, i.e., that to all intents and purposes such individuals behave as if they were Rh negative. One instance of isoimmunization was observed in an Rh₁ individual. This patient who was Hr negative, developed anti-Hr immune bodies of a degree sufficient to produce typical erythroblastosis in her second child. Further related details of the case are to be presented in a future report. It is worthy of note that the expected theoretical incidence of Hr negativity in the Rh-positive group was about 20 per cent, or 2,100 women. The occurrence of only one case of isoimmunization is an index of the weak antigenicity of the Hr factor.¹³

TABLE II. DISTRIBUTION AND INCIDENCE OF RH-ISOIMMUNIZATION IN TOTAL FEMALE GROUP

| TOTAL RH-POSITIVE WOMEN | TOTAL RH-POSITIVE SENSITIZED WOMEN | PER CENT OF RH-POSITIVE SENSITIZED WOMEN | TOTAL RH-NEGATIVE WOMEN* | TOTAL RH-NEGATIVE SENSITIZED WOMEN | PER CENT OF RH-NEGATIVE SENSITIZED WOMEN |
|-------------------------|------------------------------------|--|--------------------------|------------------------------------|--|
| 10,500 | 10 | .095% | 1,775 | 86 | 4.84% |

*One hundred forty Rh-negative women of this group had Rh-negative husbands. See Text.

III. Incidence of Erythroblastosis Fetalis

Of the total of 96 women included in this study, the outcome of pregnancy is known in 79 instances. The remaining group of 17 patients include seven who are still pregnant at the time of preparation of this report, and hence the outcome of whose pregnancy is not known now, and 10 who were either not available for serial studies or who aborted early in pregnancy.

Fifty-three, or 67.1 per cent, of the 79 patients referred to above gave birth to infants with varying manifestations of erythroblastosis fetalis.* A surpris-

*The term erythroblastosis fetalis is used in a generic sense to designate all evidences of fetal or neonatal hemolytic disease resulting from erythrocytic antigenic incompatibility between mother and fetus. Clinical manifestations include anemia, erythroblastemia of significant degree, icterus, hepato- and splenomegaly, hydrops, etc.

Comment is made below concerning the influence of technical procedural variations on antibody titer. Twenty-seven patients in the former group had a serum titer of between one and ten units* at term. Twenty-five, or 92.6 per cent, of the infants in this group survived while two, or 7.4 per cent, died. Nineteen patients demonstrated serum conglutination titers between 10 and 100, and in this group only three, or 15.8 per cent, of the infants survived, while 16, or 84.2 per cent, died. In a group of seven patients with serum titers ranging between 100 and 1,000 units, only one infant survived and six died neonatally. Two patients were observed with an antepartum titer of over 1,000. The offspring in both instances did not survive.

Our present series is too small to warrant dogmatic inferences. However, one cannot fail to note the very definite correlation between antibody titer and outcome of pregnancy. The accumulation of further studies of this type will ultimately provide a yardstick for the guidance of the obstetrician in the management of the Rh-negative sensitized woman.

The technical aspects of the serum conglutination test which has been utilized for these quantitative studies are still in somewhat of a state of flux. Wiener believes that the visible cohesion of erythrocytes which constitutes the conglutination phenomenon is brought about by the presence of an "x protein" in the serum.⁵ The substitution of plasma for serum as suggested by Wiener results usually in a higher titer. At times the plasma conglutination test may lead to the detection of a low titer of antibodies when none can be demonstrated by the serum technique. Wiener,⁹ therefore, believes that the former is the more sensitive procedure. However, it should be noted that prognostic evaluation of antibody titer, as determined by the serum conglutination test, is not equivalent to a similar titer when obtained by the use of plasma. Observation of the data presented in Table VI indicates that serum conglutination titers of over 10 units connote a high incidence of neonatal mortality; whereas such serious import becomes apparent only in higher plasma conglutination titers. In the 40 patients studied by the plasma conglutination technique, significant infant mortality was noted only when maternal plasma titers were somewhat higher.

TABLE VI. CORRELATION OF PREPARTUM ANTIBODY TITER WITH NEONATAL MORTALITY IN FIFTY-FIVE SENSITIZED WOMEN—SERUM CONGLUTINATION TEST

| ANTIBODY TITER (UNITS) | LIVED | | DIED | |
|---------------------------|--------|----------|--------|----------|
| | NUMBER | PER CENT | NUMBER | PER CENT |
| 1-10 | 25 | 92.6% | 2 | 7.4% |
| 10-100 | 3 | 15.8% | 16 | 84.2% |
| 100-1000 | 1 | 14.3% | 6 | 85.7% |
| Above 1000 | 0 | 0 | 2 | 100.0% |

Other vehicles for suspension of test cells have recently been suggested. Among these is bovine albumin solution.⁸ Preliminary observations in our laboratory indicate an even greater sensitivity, using this technical modification. Correlation of antibody titer with neonatal disease using the latter procedure remains to be determined. Such studies are under way at present. Levine has commented recently²⁶ upon the use of gum acacia, certain varieties of gelatin, polyvinyl alcohol, and even commercial mucilage in the conglutination test. Quantitative data with these substances are quite scanty at present. Nevertheless, their successful use in the conglutination reaction would appear to cast doubt upon the concept that plasma or serum contains a specific substance, conglutinin or "x protein," which is necessary for completion of the antigen-antibody reaction. There is no

*The term, unit, indicates the reciprocal of the titer. Thus a serum titer of 1:10 would be expressed as 10 units of antibody.

erythroblastotic infants failed to demonstrate antibodies in their sera by ordinary saline agglutination techniques.²⁰ The detection of antibodies in such cases was facilitated following the studies of Race²¹ in England, and Wiener⁶ and Diamond²² in this country. By special techniques, an antibody was shown to be present which was of definite pathogenetic significance. It is variously referred to as an "incomplete," "univalent," "blocking," or "inhibitor" antibody or "glutinin." In spite of the variegated terminology, there is no doubt as to its etiologic importance. This antibody, although adsorbed upon the red cells, fails to produce visible agglutination of erythrocytes when saline is used as the standard diluent medium. Its presence can now be detected in every instance of isoimmunization by the conglutination test, using serum, plasma, or albumin as diluents, or, more recently, by the use of a rabbit anti-human, globulin serum.²³ The use of saline suspensions is avoided in the conglutination test and its modifications.

In the 96 patients included in this series, 65, or 67.7 per cent, demonstrated only univalent antibodies; 23, or 24.1 per cent developed solely agglutinins or bivalent antibodies; while 8 or 8.3 per cent showed a mixture of both varieties (Table V).

TABLE V. TYPE OF ANTIBODIES IN NINETY-SIX SENSITIZED PATIENTS

| TYPE | NUMBER OF CASES | PERCENTAGE OF TOTAL |
|------------------------|-----------------|---------------------|
| Univalent | 65 | 67.7% |
| Bivalent | 23 | 24.1% |
| Univalent and bivalent | 8 | 8.3% |
| Total | 96 | 100.1% |

The terminology now in use cannot be considered entirely definitive or permanent. Much remains to be learned concerning the biological properties and mode of action of these antibodies. Because of the demonstrated higher incidence of glutinins, information pertinent to their physico-chemical properties is of interest. Coombs and Race,²⁴ in a study of univalent antibodies, noted the following characteristics: (1) a molecular weight greater than 30,000; (2) greater thermostability than the bivalent variety; (3) their preferential adsorption by Rh antigen when added to serum which contains both types of antibodies. Wiener²⁵ has postulated that they have a smaller molecular weight than agglutinins and hence traverse the placenta with greater ease. He has likewise subdivided the clinico-pathologic manifestations of erythroblastosis into two syndromes dependent upon the occurrence of either univalent or bivalent antibodies in the maternal serum. Differences in therapeutic approach are a corollary of this subdivision.⁹

V. Correlation of Prepartum Antibody Titer With Neonatal Mortality

The availability of sensitive testing procedures now assures the practically universal detection of maternal isoimmunization, but gives rise to other practical clinical problems. Reference to the literature reveals only broad generalities in regard to the prognostic significance of maternal antibody titers. However, the continued demonstration that isoimmunization does not necessarily mean neonatal disease makes the establishment of some criteria imperative.

Frequent prenatal serum studies on a sufficiently large group of patients offers the only feasible method by which such standards can be established. An analysis of this type has been made in a group of 55 sensitized women (Table VI). Repeated quantitative conglutination tests were performed using serum as the vehicle for suspension of the Rh-positive test cells. In 40 patients parallel studies were also made with plasma substituted as the suspending vehicle.

In the group of 22 patients who showed no titer increase during pregnancy, eleven had infants with erythroblastosis fetalis. Study of these cases reveals again a distinct correlation between prepartum antibody titer and outcome of pregnancy. Seven of the eight fatalities in this group occurred in infants where maternal serum agglutination titers were greater than 10. Eleven of the group had normal infants. The infants proved to be Rh negative in six. The remaining five women with Rh-positive babies had serum titers of well under 10 units.

Stress has recently been placed upon the total duration of the isoimmunized state prior to delivery as a determinant of neonatal disease. Page, Hunt, and Lucia³¹ have found that the appearance of clinical erythroblastosis fetalis can be correlated with the total antepartum duration of maternal antibodies, when their cases were first divided into those containing small amounts of antibody, and those with larger amounts. Of 43 patients who were tested at some time prepartum in our laboratory, 19 revealed initial sensitization less than ten weeks from term, and 24 demonstrated sensitization for periods greater than ten weeks prior to delivery. In some of the latter cases, the time of initial antibody production could only be approximated because of the fact that the women were already sensitized when first studied. In the series of 19 women, only 10, or 52.6 per cent, of the infants had erythroblastosis fetalis, whereas in the latter series of 24, 17, or 70.8 per cent, of the offspring showed evidence of erythroblastosis. Actually, then, there appears to be a rough correlation between the length of time of exposure to the antibodies and the appearance of fetal erythroblastosis. That this factor is apparently only secondary to the degree of maternal isoimmunization is illustrated by the following observations: Of the group of 17 patients who showed sensitization for periods greater than ten weeks, and in which all infants developed erythroblastosis fetalis, 14 women, or 82.4 per cent, had antepartum serum agglutination titers greater than 10 units. Of 7 patients who exhibited sensitization for periods greater than ten weeks, and in which group all infants were normal, maternal antibody titers were less than 10 units.

The influence of labor upon maternal isoimmunization has been previously mentioned. In a group of 19 patients (Table VII) it was possible to compare pre- and postpartum titers. The optimum time for observation of the possible stimulating effect of a large dose of antigen has been stated to be approximately eight to twenty days postpartum.²² Owing to circumstances beyond our control, the time of study could not be entirely regulated, and serum studies were therefore made two days to sixteen weeks after parturition.

In 11, or 57.8 per cent, of the cases, a significant rise in titer was noted, and in some instances this rise was of considerable magnitude. One of our patients went from a plasma antepartum titer of 96 to a six-week postpartum titer of 196,608 units. Another rose from a serum antepartum titer of 1,024 to a six-week post partum titer of 16,384. In no case under our observation were comparable increases noted during the course of pregnancy within a like period of time.

In summary, therefore, it may be noted that: (1) Clinically detectable isoimmunization does occur during pregnancy, particularly in the last trimester. When it occurs antibodies are usually of low titer, and are associated generally with no evidence of neonatal disease, or less frequently with varying manifestations of congenital hemolytic disease, depending upon the degree of maternal sensitization. (2) Patients who show immune bodies throughout a large portion of pregnancy, particularly if the titer is significantly increased, give birth in a high proportion of cases to infants with hemolytic disease. Degree of sensitization, however, seems to be more important than duration of sensitization. (3) Labor is a potent factor in the stimulation of maternal antibody formation.

doubt that ultimately the technique of this test will be further standardized and even more exact correlation between prepartum antibody titer and the severity of neonatal disease will be possible.

VI. The Course of Isoimmunization During Pregnancy and in the Puerperium

Because of the fact that most previous studies in Rh sensitization have been made either close to term or following the birth of erythroblastotic infants, opportunities for serial observations during pregnancy have of necessity been relatively infrequent.

Nevertheless, on the basis of available clinical and experimental evidence, there now exist at least two distinct viewpoints in regard to the phase of pregnancy particularly associated with isoimmunization. Levine²⁷ feels that the process may occur during pregnancy, particularly in the last trimester. Wiener²⁸ believes that the most potent dose of fetal antigen gains access to the maternal circulation at the time of labor, when placental rupture occurs and erythrocyte-laden villi are afforded numerous avenues of entry into the maternal blood stream.

In an effort to shed more light upon this problem, the data accumulated from the study of a group of 49 women, who were tested periodically during the course of pregnancy, were analyzed. Of the group, 27 showed significant prepartum changes in antibody titer and 22 evinced no titer changes. In the former group there are 16 women who were noted to change from a non-immunized state to one of sensitization, and in 11 this transition occurred in the third trimester. The outcome of pregnancy is known in 14 of the 16 women. There were no instances of erythroblastosis fetalis in the infants of ten. The maternal serum titer in nine of these cases was below 10 units. Erythroblastosis fetalis was present in four cases, two resulting in infant deaths associated with maternal serum titers of 12 and 24 units, respectively, the others in survival of the infant with maternal titers of two and three units, respectively.

Examination of this data leads to the inescapable conclusion that placental transfer in the absence of preceding maternal sensitization does occur during pregnancy. In the majority of cases, however, the degree of sensitization thus initiated is comparatively slight, and, as we have shown, is usually not associated with neonatal disease. Infant mortality, when it occurs, is associated with a concomitant rise in maternal antibody titer.

That the potentiality for early isoimmunization exists has been demonstrated by the discovery of Rh antigen in a 48 mm. embryo by Stratton.²⁹ Levine²⁷ has noted, as the result of analogy from animal experiments, that quantities of incompatible red blood cells as small as 0.13 c.c. are sufficient to stimulate the production of anti-Rh immune bodies. Studies on the guinea pig by Flexner and Gellhorn³⁰ indicate that during the latter part of pregnancy increased permeability of the placenta to water and sodium as measured by radioactive isotopes regularly exists; it would seem probable by analogy that greater opportunities for antigen transfer likewise occur during the same period.

Experimental studies, therefore, are quite compatible with the thesis that prepartum antibody changes do occur, and the present clinical study substantiates this. However, lack of sufficient numbers in the present series serve to emphasize the fact that this opinion is of a preliminary nature, and will be augmented only by subsequent observations.

Eleven patients in the group of 27 who demonstrated titer changes were found to be immunized at the time of the first serum study. The serum titers in all instances were greater than 10 units at some time prior to delivery, and in all cases erythroblastosis fetalis was present in the offspring. Fatalities occurred in nine of the eleven cases.

It is obvious that Rh antibodies in common with other immune bodies persist in the circulating blood and can be demonstrated for a long time after the initial antigenic stimulation. Davidsohn³² demonstrated antibodies in a patient six years after she had given birth to an erythroblastotic infant. Even when antibodies are no longer demonstrable *in vitro*, the altered reactivity of the body can be demonstrated by an anamnestic response to repeated stimulation years after the initial antigenic stimulus. An excellent illustration of this situation is the case cited by Levine.³³ His patient, a 20-year-old Rh-negative primigravida, who fourteen years before had received several transfusions of her father's Rh-positive blood, gave birth to a hydropic infant.

It has been noted that with the establishment of an immunized state, successive pregnancies will lead to the birth of Rh-positive infants with increasingly severe manifestations of erythroblastosis fetalis.^{28, 34} Our experience corroborates this observation. In a group of 14 women who gave histories of the birth of erythroblastotic infants previously, 13 were delivered of similarly affected children in the current pregnancy.

These observations tend to emphasize two points of important clinical significance: (1) the necessity of avoidance of unwitting sensitization of Rh-negative females by the administration of Rh-positive blood; (2) the relative inadequacy of routine crossmatching procedures in detecting isoimmunization. Both may be avoided by the routine administration of Rh-negative blood to Rh-negative females. Should it prove necessary in extreme emergency to give Rh-positive blood to such a patient, the conglutination technique should be substituted for the usual crossmatching procedure. This, at least, reduces the immediate danger of hemolytic reactions of varying degrees of severity.

VIII. Correlation of Parity With Initial Evidence of Rh-Isoimmunization

A clear distinction has been made between the incidence of Rh-isoimmunization and that of erythroblastosis fetalis. Our studies as well as those previously cited¹⁴⁻¹⁶ indicate that sensitization may occur without the production of obvious disease in the offspring. Most previous reports have been concerned with the time of initial appearance of clinical erythroblastosis fetalis. Only by the routine prepartum serologic study of large groups of Rh-negative women is it possible to detect minute subclinical amounts of antibody.

Examination of our material reveals that isoimmunization, like erythroblastosis, is essentially a phenomenon associated with multiparity. However, it is interesting to note that our data indicate that sensitization occurs, in a high percentage of instances, at an earlier date than was hitherto realized (Table IX). Of the group of 96 sensitized women in this series, 86 were multigravidas and ten were primigravidas. Six of the ten primigravidas had a definite history of prior transfusion. In the remaining four no such history could be elicited. The possibility of iso-immunization still exists in these instances, perhaps associated with a forgotten injection of whole blood intramuscularly in childhood as suggested by Levine.³³ All infants in this group of primigravida survived and in only three were there mild evidences of hemolytic disease. Again it must be emphasized that in all instances but one, maternal antibody titers were below 10 units. The one patient with an antibody titer of 32 gave birth to an Rh-negative baby and it is certain that the immune bodies found were remnants of previous sensitization.

In multigravida the initial appearance of isoimmunization was gauged by the following criteria: (1) the detection of antibodies during the current pregnancy, and (2) an unmistakable history of hemolytic disease in a previous pregnancy. A number of patients in this group gave histories of early spontaneous

TABLE VII. PRE- AND POSTPARTUM OBSERVATIONS OF ANTIBODY TITER IN NINETEEN SENSITIZED WOMEN

| CASE NUMBER | ANTEPARTUM TITER | | | POSTPARTUM TITER | | | TIME OF POSTPARTUM OBSERVATION |
|----------------|------------------|-------|--------|------------------|-------|--------|--------------------------------------|
| | PLASMA | SERUM | SALINE | PLASMA | SERUM | SALINE | |
| 2 | 96 | 8 | 0 | 196608 | | 0 | 6 Weeks |
| 3 | 2048 | 512 | 3 | 2048 | 768 | 2 | 6 Weeks |
| 5 | | 32 | 32 | | 192 | 192 | 16 Weeks |
| 12 | 24 | 8 | 0 | 3072 | 256 | 3 | 10 Days |
| 13 | 2048 | 512 | 0 | 2048 | 768 | 0 | 10 Days |
| 14 | 8 | 6 | 0 | 96 | 24 | 0 | 10 Days |
| 20 | | 16 | 0 | | 16 | 0 | 5 Days |
| 24 | 8192 | 1024 | 0 | 49152 | | 0 | 12 Weeks |
| 31 | | 768 | 0 | | 1024 | 0 | 6 Weeks |
| 33 | 8 | 3 | 0 | 32 | | 0 | 2 Days |
| 37 | | 64 | 64 | | 64 | 32 | 10 Days |
| 38 | | 3 | 0 | | 6 | 0 | 4 Days |
| 42 | 256 | 96 | 0 | 384 | 128 | 0 | 16 Weeks |
| 43 | 6 | 4 | 0 | 8 | 6 | 0 | 3 Days |
| 46 | | 16 | 0 | | 64 | 0 | 7 Days |
| 48 | | 3 | 0 | | 12 | 0 | 6 Weeks |
| 50 | 256 | 128 | 6 | 2048 | 768 | 16 | 10 Days |
| 62 | 1024 | 1024 | 1024 | | 16384 | 16384 | 6 Weeks |
| 74 | | 8 | 0 | | 48 | 16 | 6 Days |

VII. Postpartum Persistence of Antibodies

Eighteen patients in our series were not pregnant at the time serum studies were made (Table VIII). The last pregnancy had occurred one to sixty months prior to examination. Eleven of these individuals exhibited univalent antibodies, six bivalent antibodies, and one had antibodies of both varieties. Titers varied from 3 to 49,152 units. One patient with no history of subsequent transfusion still had a titer of 128 units of univalent antibody thirty-four months after the last pregnancy. Another patient demonstrated 49,152 units of univalent antibodies three months postpartum.

TABLE VIII. POSTPARTUM PERSISTENCE OF ANTIBODIES IN EIGHTEEN CASES

| CASE NUMBER | TIME POSTPARTUM OBSERVATIONS MADE (MONTHS) | TYPE AND TITER | |
|----------------|--|-------------------------------|----------|
| | | UNIVALENT | BIVALENT |
| 16 | 34 | 128 | |
| 45 | 18 | 6 | |
| 49 | 28 | | 12 |
| 56 | 60 | | 8 |
| 67 | 24 | 32 | 0 |
| 68 | 21 | | 4 |
| 71 | 14 | 12 | 3 |
| 72 | 6 | | 8 |
| 73 | 19 | Qualitative tests positive | |
| 51 | 12 | Qualitative tests positive | |
| 69 | 1 | 8 | |
| 75 | 8 | 8 | |
| 5 | 4 | | 192 |
| 24 | 3 | 49,152 | |
| 33 | 4 | 384 | |
| 41 | 5 | 384 | |
| 42 | 4 | 128 | |
| 62 | 5 | | 512 |

Aside from the definite etiologic role of Rh-isoimmunization in the causation of frank erythroblastosis fetalis, the relationship of this immune state to other pathologic phenomena associated with pregnancy or occurring in the infant is at best indefinite. The current belief, for example, that Rh heterospecificity has little, if anything, to do with the occurrence of spontaneous abortion is based largely upon work done prior to the introduction of the more sensitive tests for isoimmunization. It will be of interest to reexamine this issue in the light of further more complete data. Preliminary examination of our material indicates a statistically significant higher incidence of spontaneous abortion in Rh-negative sensitized women.³⁵ Among other problems in need of restudy with more sensitive techniques may be mentioned the relationship of undifferentiated mental deficiency and so-called physiologic icterus to subclinical sensitization.

Our studies substantiate the greater antigenic potency of the Rh₀ factor which is operative not only in pure Rh-negative women, but also in those individuals belonging to the uncommon Rh-positive categories, Rh', Rh'', and Rh'R''. The data presented also demonstrate clearly the marked predominance of so-called univalent antibodies in the serum of isoimmunized women. There is a distinct need for more fundamental studies of this immunologic phenomenon. Such investigations may have an important bearing on other aspects of clinical immunology.^{36, 37} Information concerning the mechanism of the hemolytic action of univalent antibodies is urgently needed. Studies of this nature are in progress here.

With the adoption of routine prenatal serological study of Rh-negative pregnant women, the necessity for establishment of quantitative antibody data of prognostic significance becomes evident. This has been dealt with in some detail in the present study. It is recognized that the group of cases is relatively small. Nevertheless, the inverse ratio between elevation of titer and survival of offspring seems significant.

The fluctuating technical status of the conglutination test at present leaves much to be desired. The rapid succession of suspending vehicles for the test cells has undoubtedly resulted in increased sensitivity of the procedure. The longest experience has been with serum suspended cells and hence this procedure, at the moment, offers a more certain foundation for prognostication based on antibody titer. However, the routine use of bovine albumin solution, which has proved very sensitive in our hands, may eventually supplant other techniques.

No attempt has been made in this paper to discuss either the morbid anatomic features of erythroblastosis fetalis or its therapy. In spite of the clarification of many of the basic mechanisms in this disease within the past five years, the mortality still remains quite high. Almost two-thirds of the erythroblastotic infants delivered by isoimmunized women in the present series died. This may be due in part to an insufficient understanding of the physiologic and biochemical abnormalities which exist in these afflicted infants. In part, it is also, undoubtedly, due to irreversible damage to the fetus by the time it is born. Lack of a standardized therapeutic technique is certainly an important contributing factor. The long range view, it would seem, demands an attack upon the problem from a preventive standpoint.

TABLE IX. CORRELATION OF PARITY WITH INITIAL EVIDENCE OF RH-ISOIMMUNIZATION IN EIGHTY-FOUR MULTIGRAVIDA

| PREGNANCY | NUMBER OF WOMEN | PERCENTAGE OF TOTAL |
|-----------|-----------------|---------------------|
| Second | 41 | 48.8% |
| Third | 12 | 14.3% |
| Fourth | 13 | 15.5% |
| Fifth | 2 | 2.3% |
| Sixth | 9 | 10.7% |
| Seventh | 2 | 2.3% |
| Eighth | 3 | 3.6% |
| Ninth | 1 | 1.2% |
| Tenth | 0 | 0.0 |
| Eleventh | 1 | 1.2% |
| Total | 84 | 99.9% |

abortion, fetal death in utero, or even stillbirths of undetermined etiology. These were not considered due to Rh-isoimmunization. It can thus be readily seen that the estimation of onset of isoimmunization will err, if anything, on the conservative side since some of these mishaps may have been definitely associated with Rh sensitization. Of the group of 86 multigravida, two were not available for this analysis. In 41, or 48.8 per cent, of the 84 multigravida the initial evidence of isoimmunization appeared in the second pregnancy. Initial isoimmunization in the remaining 51.2 per cent was scattered from the third to eleventh pregnancy.

No data exist in the literature at present concerning the future course of women with what may be termed minimal or subclinical Rh sensitization. It should be of great theoretical and practical interest to study the serologic behavior, in subsequent pregnancies, of the 19 patients in our series who fall into this group. At the time of writing a few such women have returned, again pregnant, for further serum studies.

Discussion

Routine prenatal Rh typing was done on 12,275 women during a thirteen-month period beginning Aug. 1, 1945. Analysis of this mass data has already yielded information of practical clinical import. In some instances the information obtained added numerical support to previous observations. Thus, the distribution of Rh types in our group corresponds closely to previously established ratios. Of great interest has been the demonstration of the incidence and behavior of Rh-isoimmunization. Current methods of serum study permit the virtually universal detection of this phenomenon. It should be noted that only the performance of serial antepartum studies permitted the detection of many instances of sensitization which would otherwise have been overlooked because antibodies were of insufficient magnitude to lead to clinically detectable disease in the newborn infant. The ultimate importance of the early detection of isoimmunization will only become manifest within the next several years as these women became pregnant again. Information can then be accumulated regarding the rapidity of development of antibody titers of sufficient degree to lead to clinical neonatal disease. Furthermore, one may then be permitted to test the thesis concerning individual variation in immunizability. Generalization on the influence of multiparity upon the incidence of erythroblastosis fetalis can be replaced by factual data.

11. The influence of labor on antibody titer was studied in 19 patients. Eleven, or 57.8 per cent, showed a significant rise in titer.

12. The duration of existence of the partum isoimmunized state, although of significance, was felt to be less important pronostically than the antibody titer.

13. Eighteen patients who were observed one to 60 months post partum were demonstrated to still have antibodies in the circulating blood. The significance of this fact for transfusion therapy and subsequent pregnancies was noted.

14. Of 96 isoimmunized women, ten were primigravidas and 86 multigravidas. Six of the ten primigravidas had a definite history of previous transfusion.

15. In 48.8 per cent of the multigravidas, the initial evidence of isoimmunization occurred with the second pregnancy. Initial isoimmunization in the remaining 51.2 per cent was scattered from the third to the eleventh pregnancy.

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Summary

1. During the first thirteen months of operation of this laboratory, Rh typing was performed as a routine part of prenatal care on 12,140 women. One hundred and thirty-five additional known Rh-negative women were referred for detailed serum studies. The distribution of Rh types in the former group conformed closely to previously established ratios.

2. In a group of 1,635 Rh-negative women whose husbands were Rh positive, 86 instances of isoimmunization, or 5.26 per cent, were observed.

Among 1,635 Rh-negative women there were 727 primigravidas and 908 multigravidas. Nine instances of isoimmunization, or 1.24 per cent, were observed among the primigravidas. Seventy-seven sensitized multigravidas were observed, an incidence of 8.48 per cent.

3. Nine instances of isoimmunization were encountered in women belonging to types Rh' or Rh''. This constituted a theoretically calculated incidence of 5.7 per cent. It was noted that individuals of these blood types behaved, to all intents and purposes, as if they were pure Rh negative.

4. One instance of Hr isoimmunization was encountered in a group of 10,500 Rh-positive women.

5. Erythroblastosis fetalis occurred in the offspring of 53, or 67.1 per cent of 79 isoimmunized women. Erythroblastosis fetalis was absent in the infants of 26, or 32.9 per cent, of this group. The fact was emphasized that the presence of Rh-isoimmunization was not necessarily synonymous with hemolytic disease in the offspring.

6. Erythroblastosis fetalis occurred once in 215 deliveries, an incidence of 0.46 per cent, in the total group of 12,275 women studied.

7. Antibody specificity was studied in 38 cases. Anti-Rh₀ immune bodies were found in 32. Four patients had antibodies of Rh₁ specificity; one, anti-Rh₂; and one, anti-Hr'.

8. In 65, or 67.7 per cent, of 96 patients only univalent antibodies were found. Twenty-three, or 24.1 per cent, developed only bivalent antibodies. Eight, or 8.3 per cent, showed a mixture of both varieties.

9. Fifty-five patients were studied in an effort to correlate prepartum antibody titers with outcome of pregnancy. When serum agglutination titers exceeded 10 units a significant infant mortality was noted. In 40 patients who were studied by the plasma agglutination technique, significant infant mortality occurred only when maternal titers were somewhat higher.

10. In a group of 49 patients in whom repeated prepartum serum studies were made several categories were observed: (a) sixteen patients changed from a nonimmunized state to one of sensitization. In 11 this occurred in the last trimester; (b) eleven patients who were immunized when first studied showed a significant rise in titer during pregnancy; (c) twenty-two patients displayed no titer increase during the entire prenatal period. A distinct correlation between maternal serum titers and neonatal disease was demonstrated in most instances.

postpartum hemorrhage. In almost every instance there were other complicating factors and the patient in these hospitals was not permitted to bleed to death without any attention. Nevertheless, the deaths in most instances had preventable factors.

Our studies indicate that proper conduct of the late second and early third stages of labor caused a marked reduction in the incidence of postpartum hemorrhage due to uterine atony, excluding patients who had a placenta previa or an abruptio placenta. We wish to stress the importance of a definite routine for the prevention and treatment of postpartum hemorrhage which will reduce the mortality to almost zero.

For many years the proper conduct of the third stage has been to wait for Ahlfeld's signs of separation of the placenta, and the usual instructions are to wait fifteen minutes to two hours or longer. Some clinicians still cling to these teachings. Warnekros in 1918 and Weibel independently in 1919, demonstrated by means of x-ray studies taken immediately (one to two minutes) after delivery, that the placenta was separated within less than five minutes after the delivery of the baby. Each investigator found little evidence of retroplacental hematoma which is supposed to separate the placenta.

Calkins, Davis, Leff, Titus, and numerous other investigators have reported that the placenta separates and can be expressed within one to seven minutes after the birth of the baby. These various reports are based on observation of thousands of cases or on actual palpation of the interior of the uterus (Leff).

Davis stated that, on our service, 16 per cent of the cases of fatal postpartum hemorrhage were due to retained placental tissue, and 36 per cent to atony (no other demonstrable cause). This latter group is much larger in the nonfatal cases and are of particular concern because a properly conducted second and third stage of labor will prevent almost all of these hemorrhages. Peckham and Kieder found that 81 per cent of the cases of hemorrhage were due to atony.

Hemorrhage from the placental site is controlled, (1) by the contraction of the uterus (compressing the uterine vessels); (2) by the time the contraction is over, retraction of the muscle bundles has occurred and the vessels are permanently compressed, and (3) by clotting of the blood in these vessels. If there is no retraction—complete loss of muscle tone—bleeding will recur each time that the contraction is over, for no uterus can remain in a state of constant contraction.

Unfortunately, most clinicians still ascribe postpartum hemorrhage to mismanagement of the third stage of labor. Davis and Boynton in 1941 are the first, so far as we know, to state that the proper management of the third stage begins in the late second stage of labor. They reported that, if 0.2 mg. of ergotrate were given intravenously after the delivery of the head or of the anterior shoulder, and thirty seconds allowed for its action, in 72 per cent of their cases the placenta had separated and could be expressed within three minutes. They attributed this short third stage to the use of intravenous

THE PLACENTAL STAGE AND POSTPARTUM HEMORRHAGE

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IN AN article "Blood Transfusion and Obstetric Hemorrhage" published in 1935, I stated that the mortality from obstetric hemorrhage had not decreased in the last twenty years despite the use of blood transfusion. Another twelve years have passed and we are in the "Age of Atomic Energy," and yet women still die from hemorrhage associated with parturition. Hemorrhage caused 30 per cent of the maternal deaths which occurred in the United States in 1944 and 1945. These deaths were either preventable or had preventable factors. It is difficult to determine just how many of the deaths were due to postpartum hemorrhage. Some of the patients do not die from the hemorrhage, but their resistance is lowered to such a degree that they succumb to infection. Pastore stated that the incidence of puerperal infection increased 400 per cent if the hematocrit dropped below 30 per cent. Reports of the Children's Bureau indicate that approximately 20 per cent of the women delivered in the last trimester of pregnancy have a postpartum hemorrhage, and of these about 40 per cent die primarily from hemorrhage and shock. A report of the maternal deaths in Philadelphia indicated that over 5 per cent were due to postpartum hemorrhage.

Beecham, in 1939, stated that in a six-year period in Philadelphia, 52 women died from postpartum hemorrhage, and that 62 per cent of these deaths were preventable. He stated, "The usual story was not that of sharp, marked hemorrhage for a few minutes and then sudden death. Rather the picture brought to light by this study was one of steady, moderate bleeding over a period of several hours ending in shock and death because no one became alarmed. There was an occasional case where bleeding was sudden and great in volume with the patient going into shock rapidly, but even in such a case there was usually time for adequate treatment." He stated that the average time between delivery and death was five hours and twenty minutes, long enough for treatment. Similar comments are made by the Chicago Maternal Death Committee.

Data from representative obstetric services given in Table I indicate that the incidence of postpartum hemorrhage is somewhere between 2 and 3 per cent, and, even in these well-regulated institutions, deaths from postpartum hemorrhage, although rare, occur. During the past fifteen and one-half years we have had four deaths from postpartum hemorrhage, and during a similar period at The New York Lying-In Hospital they had eight deaths. During the past five years at The Boston Lying-in there have been four deaths from

Eli Lilly & Co., supplied 1 ml. ampules containing 1 unit of solution of posterior pituitary.

solutions of unknown content were given to the resident staff for intravenous injection during the late second and third stages of labor. These solutions either contained saline solution, 0.2 mg. of ergotrate, or one or two units of solution of posterior pituitary. The study was carried out in six-month periods in 1944, 1945, and 1946.

The data in Fig. 1 illustrates that the placenta had been expressed within nine minutes in almost all cases irrespective of the time or substance injected. These studies, with the exception of the large series of 439 patients, were made by the resident, V.M.W. The large group were delivered by all members of the resident and intern group, with only a very few by staff obstetricians.

TABLE II. DURATION THIRD STAGE OF LABOR—PATIENTS PER CENT

| INTRAVENOUS INJECTION OF 1 ML. OF: | | | | | | | | | | |
|--|---------------------------|---|--|---------------------------|---|--|---------------------------|---------------------|-----------|-----------|
| LENGTH MINUTES | AFTER 2ND STAGE | | AFTER DELIVERY OF ANTERIOR SHOULDER | | | AFTER POSTERIOR SHOULDER AND SLOW DELIVERY OF FETUS | | | | |
| | ERGOT- RATE 0.2 MG. | SOLU- TION POSTE- RIOR PITU- ITARY 2 UNITS | NACL SOLU- TION | ERGO- TRATE 0.2 MG. | SOLU- TION POSTE- RIOR PITU- ITARY 2 UNITS | NACL SOLU- TION | ERGO- TRATE 0.2 MG. | SOLUTION POST. PIT. | | |
| | | | | | | | | 2 UNITS | 1 UNIT | 1 UNIT |
| 0.2-1.0 | 6 | 13 | 7 | 30 | 29 | 13 | 35 | 43 | 50 | 42 |
| 2 | 42 | 41 | 36 | 33 | 39 | 50 | 40 | 35 | 22 | 29 |
| 3 | 30 | 28 | 19 | 23 | 18 | 27 | 15 | 14 | 18 | 12 |
| 1-3 | 78 | 82 | 62 | 86 | 86 | 90 | 90 | 92 | 90 | 83 |
| 4-6 | 17 | 15 | 28 | 8 | 9 | 5 | 5 | 8 | 10 | 13 |
| 7-9 | 5 | 1 | 10 | 2 | 5 | 5 | 3 | | | 2 |
| 10-14 | | 1 | | 2 | | | 2 | | | 1 |
| 15-19 | | 1 | | | | | | | | 1 |
| 20-29 | | | | 2 | | | | | | 2* |
| Number patients | 34 | 61 | 56 | 44 | 73 | 44 | 40 | 80 | 40 | 439 |
| Average time— minutes | 3.6 | 2.6 | 2.7 | 2.1 | 1.9 | 2.6 | 1.9 | 2.0 | 2.0 | |
| Average blood— ml: with placenta After placenta | 136 | 49 | 95 | 32 | 55 | 60 | 55 | 48 | 40 | 51 |
| | | | | | | 171 | 120 | 64 | 89 | 73 |

*Manual removal in two cases.

The figures for the duration of the third stage are given in Table II and are included to show that over 75 per cent of the placentas had been expressed within one to three minutes irrespective of time or substance injected providing the operator had been taught the proper management. If no oxytocic was used and no definite pause made in the delivery of the baby, the placenta had separated and delivered within three minutes in 80 per cent of the cases. If an injection was made with the anterior shoulder and thirty seconds allowed for its action, the placenta was delivered within three minutes in 62 per cent of the cases where saline was used and 100 per cent at the end of nine minutes. Similar figures for ergotrate and pituitary are 86 per cent at the end of three minutes and 94 per cent and 100 per cent, respectively, at the end of nine

ergotrate in the late second stage. However, all the evidence at hand indicates that the placenta normally begins to separate as the baby is born and that it can be expressed usually within one to three minutes after delivery. If the women were in the upright or squatting position, gravity would cause the early delivery of the placenta. With the patient in the supine position and usually anesthetized, external force must be used to expel the placenta.

The so-called Duncan and Schultze methods of placental separation and extrusion from the uterus are only of historical interest, and discussion should be omitted from textbooks. The retroplacental hematoma is almost non-existent if the second and third stages are properly conducted, and most obstetricians now know it has nothing to do with placental separation. We have confirmed Royston's statement that if the placenta is extruded through a tight ring (contracted uterus or vaginal orifice), it will almost invariably be a Duncan, and vice versa.

TABLE I. POSTPARTUM HEMORRHAGE

| HOSPITAL | YEAR | DELIV- ERIES | HEMOR- RHAGE INCIDENCE PER CENT | MORTALITY (CASES) |
|-------------------|------------|-----------------|--|---|
| Johns Hopkins | 1933 | 19,290 | 6.14 | 4 deaths in series (corrected) |
| Boston Lying-in | 1941-45 | 13,347 | 1.71 | 2 deaths |
| New York Lying-In | 1936 | | 6.40 | |
| New York Lying-In | 1940-43 | 9,040 | 1.94 | 6 deaths 1932-42 2 deaths 1943-45 |
| Chicago Lying-in | 1933-36 | 8,100 | 2.50 | 4 deaths 1931-42 0 deaths 1943-46 |
| Chicago Lying-in | 1941 | 753 | 2.00 | Ergotrate in third stage |
| Chicago Lying-in | | 1,020 | 0.40 | Ergotrate with anterior shoulder |
| Chicago Lying-in | 1944-46 | 6,638 | 2.50 | Ergotrate with anterior shoulder |
| Chicago Lying-in | 1946—6 mo. | 664 | 1.36 | Ergotrate with anterior shoulder |
| Chicago Lying-in | 1946—6 mo. | 1,159 | 0.35 | Solution posterior pituitary with posterior shoulder |

Davis' technique has been the routine on our service up to the present time, but patients still continue to have postpartum hemorrhage. As indicated in Table I, the incidence for 6,638 vaginal deliveries in 1944 to 1946 was 2.5 per cent. It is true, as pointed out by Davis, that we rarely have to pack uteri for postpartum hemorrhage since using intravenous oxytocics. However, all of us—including Davis—have had patients who, despite intravenous injections of an oxytocic drug, continued to bleed from the atonic uterus. Since we still have postpartum hemorrhage due to atony and, it seems to us, a higher incidence of delayed hemorrhage occurring five to twenty days after delivery, we began to restudy the conduct of the late second and third stages of labor.

Leff, in 1945, reported that the action of ergotrate was different from that of solution of posterior pituitary, and believed that the latter solution was preferable until the placenta had been expelled from the uterus. A number of investigators have compared the effects of intravenous injections of ergotrate with intramuscular injection of pituitary solution. No one, so far as we know, has injected both of these oxytocics intravenously. Numbered

Our studies indicate that the separation and delivery of the placenta in anesthetized patients can be completed in over 95 per cent of the cases within six minutes after delivery with or without any oxytocic drug if the baby is delivered slowly. However, if no oxytocic is used either during the second or third stage of labor in these patients, the amount of blood lost with the placenta is slightly increased and the blood loss after the expulsion of the placenta is definitely increased. It, therefore, is obvious that anesthetized patients must be given an oxytocic.

Stander does not mention any length of time for the actual delivery of the baby. He states that the placenta begins to separate as the baby is born. According to him the average length of the third stage is four to seven minutes, but he also states that one should wait at least one hour for the delivery of the placenta, during this time trying repeated Credé maneuvers under anesthesia, if necessary.

Greenhill writes that after delivery of the baby's head one should wait for uterine contractions to help with the remainder of the baby, this requiring maybe one or two minutes. After delivery of both shoulders, the rest of the baby is born with one pain. He states, "Do not pull it out, but let the uterus expel it." According to him the placenta separates in a few minutes but he also advises waiting one hour, repeatedly trying the Credé expression.

Beck states that the shoulders should deliver spontaneously unless the patient is anesthetized. If there are no signs of placental separation in one hour, he advises the Credé maneuver. The placenta, according to him, should be delivered in three to four hours. No times are given for the delivery of the baby and no time for the length of the third stage.

Calkins states that in 69 per cent of the cases it was separated in less than five minutes.

The doctor must watch the uterus closely, and as soon as Calkin's sign is present—persistence of a globular uterus—the placenta is expressed by the Pastore technique with slight traction on the cord once the placenta is in the vagina. If one waits too long, the muscular portion of the uterus may contract about a portion of the placenta and make the expression difficult. If this happens, the placenta which is almost always protruding into the upper vagina, can be grasped with the sterile gloved hand and gently extracted. All placentas are removed manually if necessary at the end of one hour maximum, and usually within fifteen minutes. *If there is hemorrhage, the placenta is expressed or removed manually at once.*

Ninety per cent of 900 patients had a third stage of three minutes or less, and in 98 per cent of some 2,000 patients, it was less than nine minutes.

Davis and Boynton stated that in 1,020 patients who received an intravenous injection of ergotrate with the anterior shoulder, 81 per cent had a measured (with a graduate) blood loss of less than 100 ml. with the placenta. Only four, or 0.4 per cent, lost more than 500 milliliters. Seven hundred fifty-three patients received the ergotrate after the second stage, and only 35 per cent lost less than 100 milliliters. Two per cent lost more than 500 milliliters.

minutes. Obviously in the majority of cases the oxytocic had no effect in the separation or delivery of the placenta.

Slow delivery of the fetus seemed to be the factor which favored the separation of the placenta. Obviously the uterine wall requires some time to readjust itself to the decreasing size of its cavity as the baby is expelled. Our next experiment was to deliver the anterior shoulder, wait thirty seconds, deliver the posterior shoulder, inject 1 c.c. of the unknown solution, wait thirty seconds, and then slowly deliver the baby. The baby was removed, and usually the placenta could be expressed without any difficulty. It has required considerable effort to keep the house staff from hurrying the delivery of the baby once the head has been born.

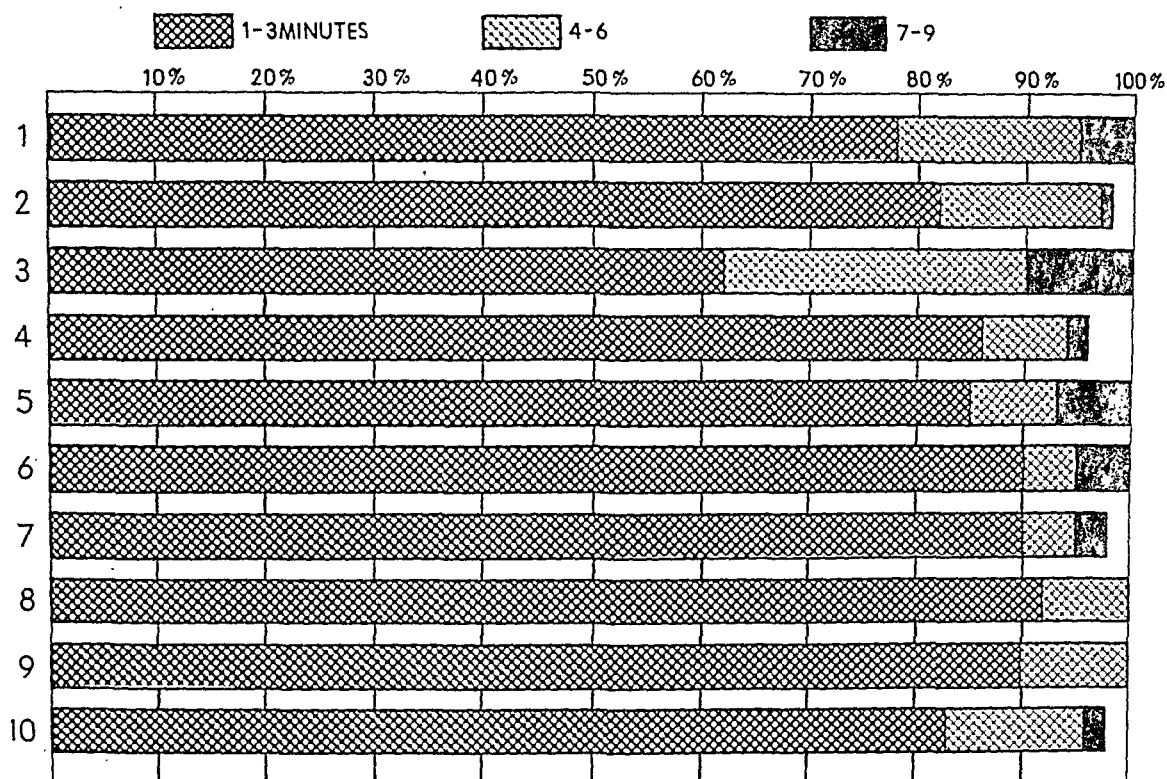


Fig. 1.—The duration of third stage of labor. Per cent of patients. Intravenous injection after second stage. 1. Ergotrate 0.2 mg. 2. Solution of posterior pituitary 0.2 ml. (2 units), after anterior shoulder. 3. Saline solution. 4. Ergotrate 0.2 mg. 5. Pituitary 0.2 ml., after posterior shoulder. 6. Saline solution. 7. Ergotrate 0.2 mg. 8. Pituitary 0.2 ml. 9. Pituitary 0.1 ml. 10. Pituitary 0.1 ml. and 0.4 mg. ergotrate intramuscularly after third stage.

Since most of our patients are anesthetized, the strength and frequency of the uterine contractions and especially the use of the abdominal muscles are minimal. Where the patient is given only gas with each pain and no traction is made on the baby, the total time from the delivery of the head to the complete expulsion of the baby requires on an average in multiparas four and one-half minutes. The average slow delivery time for primiparas under anesthesia is three and one-fourth minutes with the technique described. The placenta was delivered in 90 per cent to 92 per cent of the cases within three minutes after the delivery. Usually the placenta was in the lower segment and vagina within less than one minute and could be readily extracted without any difficulty with a minimal blood loss.

nique) rather than to the ergotrate. Intravenous injections of pituitary solution are active at any time during labor or the early puerperium.

Fig. 3 illustrates the percentage of patients with uterine blood loss occurring during the five to sixty minutes after the placenta had been expressed. This uterine blood is in addition to the placental blood. The relaxation of the uterus (partly due to the anesthesia) when saline was used, resulted in increased bleeding with 2 per cent having postpartum hemorrhage, and an additional 12 per cent losing 300 to 499 ml. The large series of 439 patients delivered by various members of the house staff offers the best illustration of the value of pituitary and slow delivery of the baby. Ninety-three per cent of the patients lost less than 200 ml. of blood, and 78 per cent lost less than 100 milliliters. The average blood loss with the placenta was 51, and after the placenta, 73, a total of 124 milliliters.

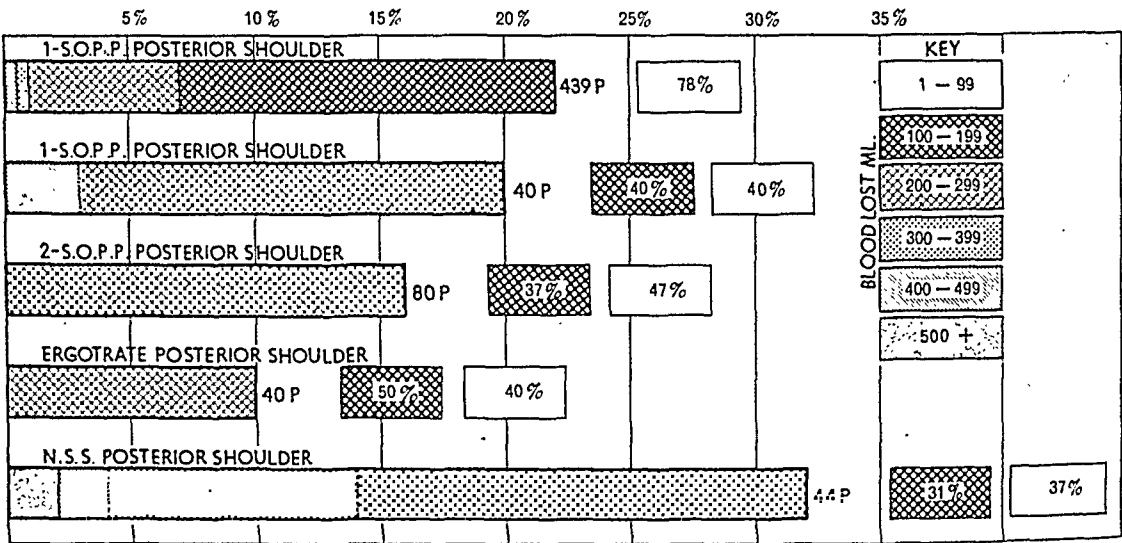


Fig. 3.—Measured blood loss after the placenta. Per cent of patients. Intravenous injection after posterior shoulder.

We had been using two units or 0.2 ml. of pituitary solution. The dose was decreased to one unit in 1 ml. of normal saline (1 ml. pituitary or pitocin and 9 ml. saline) and the final series of 439 cases was as outlined with the injection of one unit of pituitary after the posterior shoulder and, after the placenta was delivered, the injection of 0.4 mg. of ergotrate intramuscularly. There were no postpartum hemorrhages with the placenta or after the placenta, but there were a few cases of hemorrhages of 300 and 400 c.c. The number is extremely small and the blood could have come from the episiotomy or from vaginal or cervical lacerations. Some unquestionably came from the uterus which in certain cases relaxes—especially if the patient is deeply anesthetized. However, the results on the whole were better than they had been in the past.

The data in Fig. 4 are based on an exact determination as acid hematin and conversion into ml. of patient's blood of all the blood lost with the placenta and during the first hour post partum (vaginal pack) with various

Fig. 2 shows that 95 per cent of the patients on whom the oxytocic was used after the posterior shoulder with slow delivery of the fetus, had a blood loss with the placenta of less than 100 c.c. with no postpartum hemorrhage, and 44 per cent had less than 100 ml. after the placenta, again with no postpartum hemorrhage. It is obvious that one must be very cautious about interpreting results; for example, saline solution with the anterior and posterior shoulders resulted in 75 and 81 per cent respectively, of the patients having less than 100 ml. However, the percentage of patients with blood losses of 200 ml. and more was increased. Ergotrate and pituitary are obviously better than saline.

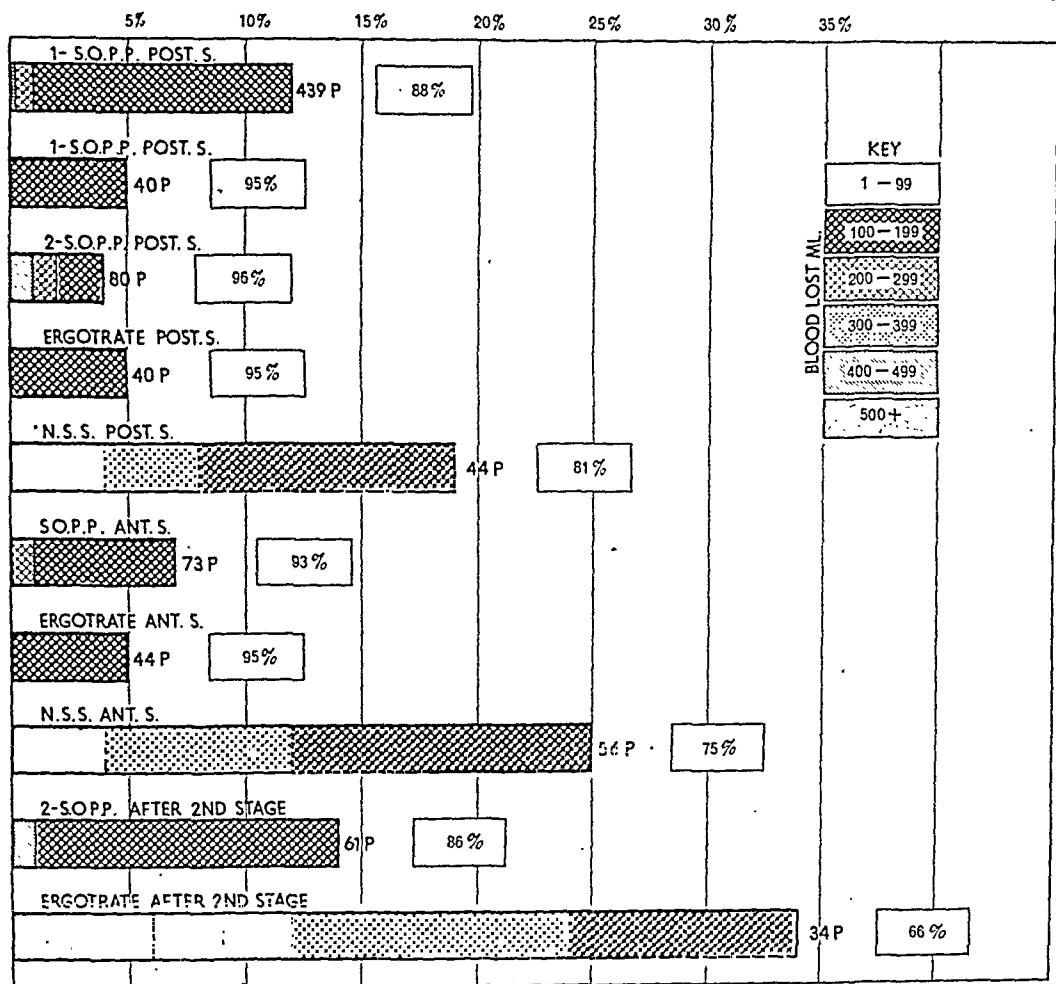


Fig. 2.—Measured blood loss with placenta. Per cent of patients. Intravenous injections.

The average blood loss for each substance used is given in Table II. The loss was less than 100 ml. for all substances, including saline if there was some delay in the delivery of the fetus. Pituitary after the second stage resulted in an average blood loss of 49 ml., while ergotrate had 136 milliliters. Davis has stated that ergotrate is more effective if injected during the second stage than after delivery. Our data indicate that the effective reduction of blood lost with the placenta is due to the pause during the delivery (Davis tech-

shoulder, and the incidence of postpartum hemorrhage was 0.35 per cent as compared with 1.36 per cent in 664 patients delivered by the staff obstetricians. Obviously the figures are similar to those obtained by Davis in 1941. Whether the decrease is again due to the special emphasis on the third stage or whether pituitary solution with the posterior shoulder is responsible, can only be determined over a period of years. We believe that intravenous injections of pituitary are much more efficacious in producing uterine contractions than ergotrate, but the latter has a longer action. *Nothing is gained by waiting hours for the separation of the placenta and our resident staff is instructed, if there is no bleeding, to remove the placenta manually within one hour at a maximum and usually within fifteen minutes after delivery.* The only exception to this rule is where there is very definite evidence of external infection on or about the vulva such as extensive contamination of the perineum with feces, a Bartholin abscess, etc.

The senior author has been advocating manual removal of the placenta as a teaching procedure for many years, and during the past six months there were 80 manual removals of the placenta and 12 explorations of the uterus; in the same period a year ago there were 18 manual removals and two explorations. The majority in the recent period were for teaching purposes. The hospital morbidity was 7.9 per cent, and for the same period in 1945, 9.2 per cent. We believe that the only way one can learn how to remove the placenta manually is to do it in normal cases under supervision. If doctors would learn this procedure, they would not be removing omentum and intestine mistakenly for placenta. They would also be able to recognize the rare case of adherent placenta; inversion of the uterus, incomplete rupture of the uterus, and myomas within the uterus.

Dieckmann and Daily reported in 1935 that the average total blood loss (episiotomy plus uterine) was 342 milliliters. Odell and Seski, in a study on our service, found that the average blood loss from an episiotomy was 253 milliliters. They found an average blood loss of 16 to 57 ml. per minute with a total blood loss of 28 to 339 ml. just from the episiotomy. Our data indicate that most patients lose approximately 51 ml. with the placenta and 73 ml. after the placenta; and, if there has been an episiotomy or extensive laceration, an additional 250 ml. or more making a total of approximately 370 ml. or more of blood in presumably normal deliveries (episiotomy). The pregnant woman does not have an extra supply of blood which will permit her to lose excessively at delivery. The withdrawal by venisection of 500 ml. of blood from patients immediately after delivery can be detected by changes in the blood within five minutes, and within twenty-four hours each patient showed an appreciable drop in hemoglobin, hematocrit, and serum protein concentration. These two facts indicate that a slightly excessive amount of blood loss at delivery will inevitably mean that the total blood loss is well over 500 ml. of blood.

All the vulvar pads, as well as the thick pads that are placed beneath patients, were saved for a period of twenty-four hours and the blood within them determined as acid hematin. The average blood loss for a large number

methods of managing the second stage and with different oxytocic drugs. The data shows that the amount of blood lost with the placenta is greatest with rapid delivery of the fetus without an oxytocic, and that as the delivery of the fetus is prolonged and, especially if oxytocics are used, the blood loss becomes minimal. Pituitary seems to be slightly better than ergotrate, but the number of cases is too small to warrant any conclusion. It has seemed to us that 0.2 mg. of ergotrate intravenously is too small a dose, and all patients are now being delivered with the slow technique but using 0.4 mg. of ergotrate intravenously after the posterior shoulder and the same dose intramuscularly after the delivery of the placenta. Our object is to determine the best drug which will aid in preventing postpartum hemorrhage. We believe the conduct of the third stage entails the slow delivery of the baby if there are to be no complications with the placenta.

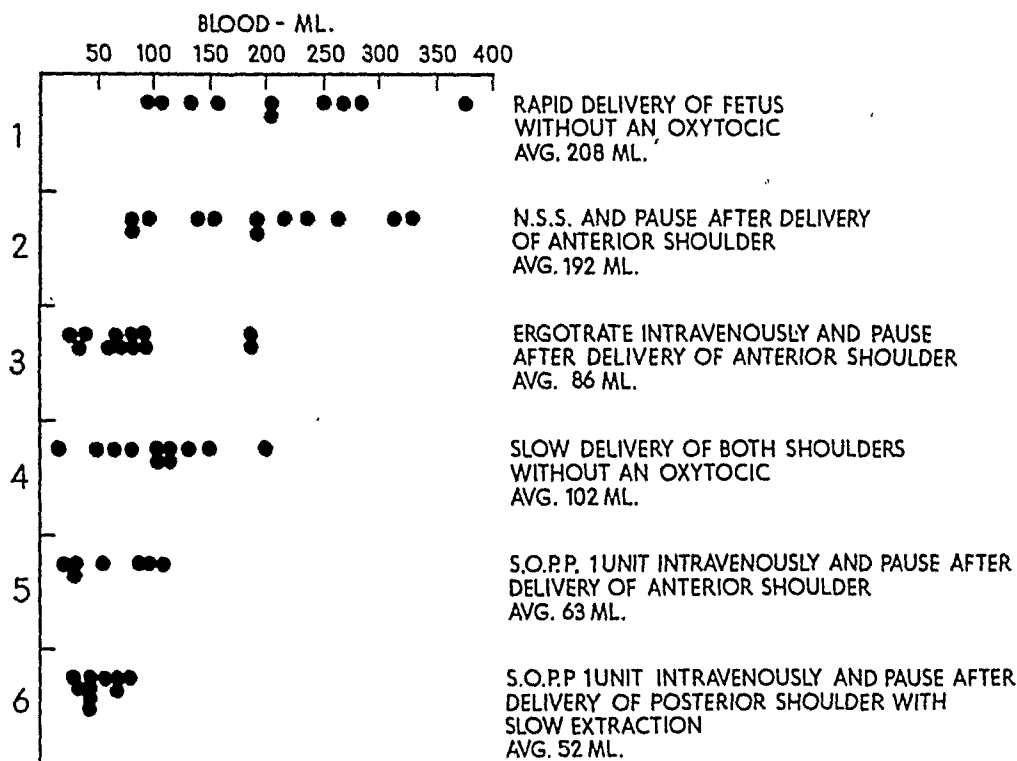


Fig. 4.—Acid hematin determination of blood lost with placenta and on packs for one hour after delivery under various managements of the late second and third stages of labor.

Davis and Boynton reported in 1941 that the incidence of postpartum hemorrhage in 753 patients who received no oxytocic in the second stage was 2.0 per cent as compared with 0.4 per cent in 1,020 patients who were given 0.2 mg. ergotrate intravenously with the anterior shoulder. This technique has been followed but the incidence of hemorrhage was 2.5 per cent in vaginal deliveries in 1944 to 1946. Pastore has defined postpartum hemorrhage as a blood loss amounting to 1 per cent or more of the body weight. Our criteria has always been 500 ml. or more, and we believe all blood losses of 300 ml. or more are abnormal. During the last six months of 1946, 1,159 patients were delivered by the house staff, using one unit of pituitary with the posterior

one imitates the normal mechanism of labor, results will be markedly improved. For a proper separation of the placenta, it is of the utmost importance that the baby be delivered slowly—in stages with a thirty to sixty second pause after the delivery of each shoulder—requiring a total of at least three minutes. Thus the uterine wall is given time to *contract and retract* thereby tearing itself away from the placenta. The latter has usually separated within less than one minute. After the fetus has been expelled, and as soon as the uterus retains its globular form, it should be compressed but not pushed into the pelvis. When the placenta is in the vagina it should be extracted by pulling on the cord. We do not believe that an oxytocic is necessary for the separation of the placenta; but, since patients are not under normal conditions—*anesthesia, etc.*—we believe that one unit of solution of posterior pituitary or 0.2 to 0.4 mg. ergotrate should be injected intravenously after the posterior shoulder if the doctor is experienced; if he is not, then after the delivery of the placenta. This will prevent excessive bleeding after the placenta. Our nurses give many of the intravenous injections.

If the placenta cannot be delivered and there is no bleeding, one may wait, at a maximum one hour, but all retained placentas should be manually removed at the end of this time.

Uterine hemorrhage is treated by the immediate removal of the placenta, manually if necessary, or after the third stage by manual palpation of the uterine cavity and visual inspection of the vagina and cervix. One of the above oxytocics should be injected intravenously and repeated one time. If the bleeding continues, the uterus must be packed. A transfusion of 1,000 ml. or more of blood, if necessary, must be given at once. Periodic hemoglobin or hematocrit determinations must be made.

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of patients during the first twenty-four hours after delivery, excluding the first hour, amounted to an average of 52 milliliters. Since the bleeding after the first twenty-four hours becomes negligible, amounting to only a few ml. of blood per day, no comparison of oxytocic drugs was made.

If the placenta has been delivered *intact* and yet bleeding still continues from the uterus, the following treatment is indicated:

1. Repeat the intravenous injection of ergotrate or pituitary solution.
2. Explore the uterus manually for an accessory placental lobe, tumors, and to exclude rupture.
3. Briskly massage the uterus through the abdominal wall.
4. Pack the uterus if bleeding continues despite 1, 2, and 3.

This systematic treatment will control uterine bleeding from atony in almost 100 per cent of the cases.

5. After the hemorrhage, the patient must be given saline solution, 1,000 to 2,000 ml., by hypodermoclysis and blood in amounts more than sufficient to replace what was lost (minimum 1,000 ml.), which is always underestimated. Serum, plasma, 20 per cent glucose and saline solutions, are only stop-gaps until blood is available. If 500 ml. of any of these solutions are injected intravenously, the blood pressure will increase and the patient improve, but the injection must not be repeated unless blood is also given.

Studies of postpartum hemorrhage occurring after the tenth day are still being continued. During the last six months of 1946 there was one curettage because of hemorrhage two weeks post partum. In preceding similar periods, the number has varied from five to twelve. Manual exploration of the uterus in these patients was given up many years ago because of the high mortality from infection. The uteri are curetted with a large dull curette. Only in rare instances has a piece of placental tissue been found. The usual finding is thrombosed vessels from the placental site. We think the delayed postpartum hemorrhage may be due to faulty involution of the placental site resulting from the ergotrate.

There have been several reports about the dangers of shock and death from injections of solution of posterior pituitary. In a rather long period of full-time obstetrics, the senior author has encountered one patient who is unusually sensitive to pituitary. He has seen infrequent reactions from this drug but none fatal or alarming other than those due to rupture of the uterus from tetanic contraction. In the present study, over 2,000 patients have received one or two units of pituitary during the terminal portion of the second or third stage of labor, and there have been no recorded reactions attributable to the drug.

Summary

The prevention of postpartum hemorrhage is much easier than the treatment. Prevention begins with the proper conduct of the terminal phase of the second stage of labor. With patients under analgesia, anesthesia, and on hospital beds, etc., one can no longer speak of normal deliveries. However, if

TOXIC COMPLICATIONS OF PREGNANCY IN GORGAS HOSPITAL, PANAMA CANAL ZONE, 1931-1945*†

An Analysis of 10,000 Pregnancies

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REPORTS on pre-eclampsia and eclampsia under tropical conditions have been few and inconclusive. In the tropics of the Western Hemisphere the only reports available show Puerto Rico and Trinidad to have some of the highest rates in the world.¹ The records of Gorgas Hospital on the Isthmus of Panama afford an unusual opportunity to evaluate the influence of race and economic conditions as well as the effects of a tropical climate on pregnancies under good prenatal care.

The Canal Zone is not only similar in climate to Puerto Rico and Trinidad, but also has two racial groups, the "Panamanians" and the West Indian Negroes, respectively, who are comparable to the chief inhabitants of these two areas and might be expected to show the same high incidence of pre-eclampsia and eclampsia. A third distinct group, the white Americans, can also be studied in Panama and the incidence of their difficulties in pregnancy compared with reports for various parts of the United States. De Snoo² has reported that Europeans living in Batavia, Java, have nearly five times as much eclampsia as do the natives, and about three and one-half times as much as the Chinese living there. The incidence of pre-eclampsia and eclampsia in Americans in Panama was therefore of considerable interest.

Recent studies³⁻⁷ have shown that the poorer nutrition of the lower economic groups may be an important factor in their generally high incidence of toxic complications during pregnancy. In Panama there are two distinct economic groups of Panamanians eligible for treatment in Gorgas Hospital. The larger of these is obliged to live on the low salary scale of the "silver" payroll. The Panamanians on the "gold" payroll receive the same relatively high wages as the Americans. This division of the employees of the Panama Canal into "silver" and "gold" is found throughout the administration of the Zone and dates back to the early construction days when laborers were paid in silver coin and the clerical and administrative workers were paid in gold. This study, because of these sharp economic distinctions, was able to investigate the role of nutrition and hygiene in the incidence of the toxemias of pregnancy in Panama.

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†The statistical analysis of the data was performed by James Rafferty, M.D., of the Department of Pathology, School of Medicine and Dentistry, University of Rochester.

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"Panamanians" in this study. In the preliminary tabulations a group of patients who could be identified as Spanish and Indian mixtures with little or no Negro ancestry were studied separately from the remainder of the silver "Panamanian" group. However, such differences as were found could not be considered significant, and this separation does not appear in the tables presented.

The original Panamanian was an Indian. To his stock for 300 years has been added the blood of Europeans, particularly Spanish, and of an indeterminate number of Chinese, Hindus, Negroes, and people of other "races." The Panamanians on the gold pay roll included very few recent European-Panamanian mixtures. Individuals with one or more recent Negro antecedents were somewhat more frequent among the Panamanians on the silver pay roll.

The Americans have come from all parts of the United States and remain for a varying length of time; some for only a year, but many spend the rest of their lives in the Canal Zone. They represent a fair cross-section of the white citizens of the United States in their racial makeup. Their economic status in the Zone is uniformly very good.

The Records.—In the *silver* clinic the prenatal records were kept chronologically in bound volumes with a page for each patient. In the *gold* clinic the same information was kept for each patient on combined obstetric and surgical history cards. During most of the fifteen-year period these clinics were under the personal direction of one man (Dr. Howard K. Tuttle). During his vacations and following his retirement in 1945 the same procedure was followed.

Blood pressures were determined at each visit by the auscultatory method using a mercury sphygmomanometer. Urine specimens were filtered and tested for albumin by layering over nitric acid. A distinct ring of precipitate was read as positive. All clinics were held in the afternoon.

Every clinic record was examined. A patient whose course suggested a prenatal irregularity or who was signed out of the hospital with any abnormality of pregnancy was carefully investigated. The final diagnosis was made with the aid of the combined clinic and hospital records. Only cases actually delivering in Gorgas Hospital were included in the final tabulation.

The total number of births and stillbirths was obtained directly from the official register of births for Gorgas Hospital. In order to learn the total number of pregnancies in each racial group, 1,243 records were examined (approximately every tenth delivery), and the patient was classified as to race in the same manner as was done for all the abnormal patients studied. The percentage of the total number belonging to each group was calculated from these figures and applied to give the group totals. The delivery records of each of the 343 stillbirths were similarly examined for racial classification.

Criteria for Diagnosis.—Any patient with a previously normal blood pressure range who showed a distinct rise of 20 mm. of Hg or more in diastolic to a blood pressure of 140/90 or higher with or without albuminuria, edema, or other signs was considered abnormal. If adequate evidence was at hand that this rise was of more than transient nature, i.e., if despite bed rest and oral magnesium sulfate, it persisted for several days in an outpatient or for several hours in a hospitalized patient, then pre-eclampsia was diagnosed. If the pressure rose and remained above 150/100 for some period of time and if there was present marked albuminuria, edema, and/or subjective symptoms of severe headache, visual disturbances, abdominal pain, dizziness, etc., the condition was diagnosed as severe pre-eclampsia.

A small percentage of cases was included as pre-eclampsia which did not meet fully the above blood pressure requirement. In these cases severe albuminuria, marked subjective symptoms, or initial hypotension seemed to

Various authors have noted seasonal changes in the incidence of eclampsia in many parts of the world. It has been associated with cool rainy weather,⁸ cool dry weather,⁹ high humidity,¹⁰ high temperatures,¹¹ warm moist weather,¹² and changeable weather.^{13, 14} Scheyer¹⁵ is unable to establish any correlation with the weather. In Panama, the temperature is remarkably uniform, but the year is divided into a rainy season and a dry season, the dry season is preceded in December and followed in May by a period of changeable weather. The rainy season extending through the second half of the year becomes progressively wetter, although there is generally considerable sunshine and clear weather each day. The possible effect of these seasonal changes on the occurrence of the toxic complications of pregnancy was investigated.

Hypertension is generally considered to be less common in the tropics. Thonnard-Neumann¹⁶ and Kean^{17, 18} have found that while this is true for the native Indian and Panamanian, the Negroes show a very high incidence of hypertension beginning at an early age. The relation of this hypertensive tendency in the Negroes to the incidence of the transient hypertension of pre-eclampsia was examined.

The present investigation studies these and related problems by an analysis of the more than 10,000 patients delivered in Gorgas Hospital in the years 1931 to 1945. The clinic and hospital record of every patient was studied, and the diagnosis made or checked by the senior author in accordance with the criteria to be described. Differences in diagnostic standards during these years do not enter appreciably into the final tabulations. We have endeavored to describe the distribution of the toxic complications of pregnancy in the population studied, although we cannot with any certainty account for many of the characteristics of this distribution. This survey was planned as a basis for further study of possible causative factors in "toxemias."

Material and Methods

The Patients.—The division of employees of the Panama Canal into "silver" and "gold" has already been noted. The Health Department also operates on this basis. In the "silver" clinics, dispensaries, and wards are seen all of the West Indian Negroes and a large proportion of the Panamanians. Their income is sharply limited by low fixed standards, housing is crowded, families are large, and life for them is a continuous economic struggle. The "gold" patients, who are largely Americans, have the advantage of premium wages, low tax free prices at Government Commissary or Post Exchanges, and generally spacious accommodations. The standards of medical care for these two groups are essentially the same. All doctors are on a full-time salary basis, and no fees are charged for their medical services. Although the hospital charges are minimal, they are frequently a difficult burden for the low income patients.

The West Indian Negroes by appearance, background, customs and language constitute a sharply defined group. Only patients who were born in Jamaica, the Barbados, or other West Indian islands, or whose parents were born there are classified in this group in the present study. In a few more years this classification will break down as present "West Indian" children born in Panama mature. Thousands of these Negroes have been imported as laborers since the early days of the canal. Social and political barriers to intermarriage with the "Panamanians" are often broken, and many patients in our series are really mixtures of these two strains. Such patients are included with the

TABLE I. INCIDENCE OF MAJOR TOXIC COMPLICATIONS OF PREGNANCY IN GORGAS HOSPITAL, 1931 TO 1945*

| TOTAL DELIVERIES† | GOLD ROLL (HIGH INCOME) | | | | SILVER ROLL (LOW INCOME) | | | |
|---|-------------------------|-------------|-------------|-------------|--------------------------|-------------|-------------|-------------|
| | AMERICAN | | PANAMANIAN | | PANAMANIAN | | WEST INDIAN | |
| | 2,052 | | 935 | | 2,123 | | 5,050 | |
| | NUM- BER | PER CENT | NUM- BER | PER CENT | NUM- BER | PER CENT | NUM- BER | PER CENT |
| Mild pre-eclampsia | 70 | 3.4 | 26 | 2.8 | 82 | 3.8 | 313 | 6.2 |
| Severe pre-eclampsia | 13 | 0.6 | 11 | 1.2 | 29 | 1.4 | 93 | 1.9 |
| Ante- and intrapartum eclampsia | 1 | 0.05 | 9 | 0.96 | 10 | 0.47 | 23‡ | 0.46 |
| Postpartum eclampsia | 1 | 0.05 | 2 | 0.21 | 5 | 0.24 | 9 | 0.21 |
| Hypertension with superimposed pre-eclampsia | 6 | 0.3 | 0 | 0 | 15 | 0.7 | 48 | 0.9 |
| Hypertension apparently uninfluenced by pregnancy | 2 | 0.1 | 5 | 0.5 | 8 | 0.4 | 47 | 0.9 |
| Therapeutic abortion for hypertension§ | 1 | - | 0 | - | 1 | - | 7 | - |
| Albuminuria | 3 | 0.15 | 0 | 0 | 13 | 0.6 | 20 | 0.4 |

*One silver and four gold patients with definite hypertension but with inadequate data recorded in their clinical records to show the nature of this hypertension are not included in this table.

†Based on a racial sampling of 1,236 patients which yielded: 225 Americans, 116 Gold Panamanians, 264 Silver Panamanians, and 628 West Indians..

‡Since these are not included in the total patients beyond the fifth month of gestation delivering in hospital, the percentage incidence cannot be calculated.

§Includes four hypertensives with superimposed eclampsia.

TABLE II. THE PROBABILITY OF SIGNIFICANT DIFFERENCES BETWEEN GROUPS*

| | GOLD VS. SILVER | | AMERICAN VS. GOLD PANAMANIAN | | SILVER PANAMANIAN VS. WEST INDIANS | | GOLD PANAMANIAN VS. SILVER | | |
|-------------------------|-----------------------|--------|------------------------------------|------|---|------|-------------------------------|-------|------------|
| | | | | | | | PANAMANIAN | | LIABILITY‡ |
| | χ^2 † | P | χ^2 | P | χ^2 | P | χ^2 | P | P |
| 1. Mild pre-eclampsia | 18 | <.0001 | .5 | .5 | 11 | .001 | 1 | .3 | .1 |
| 2. Severe pre-eclampsia | 11 | .001 | 2 | .2 | 2 | .2 | .1 | .9 | .1 |
| 3. Eclampsia | 3 | .08 | 12 | .001 | .1 | .9 | 1 | .3 | .04 |
| 4. Hypertension | 23 | <.0001 | .1 | .9 | 5 | .020 | 1.6 | .2 | .015 |
| 5. Albuminuria | 6 | .015 | Binomial§ | .3 | 1 | .3 | Binomial‡§ | <.001 | .7 |

*Certain of the categories of Table I have been combined for statistical analysis. "Significant" probabilities are italicized.

† χ^2 for Gold vs. Silver and for other comparisons has 1 d. of f. as calculated from a 2 x 2 contingency table using Yates Correction.

‡Liability is the probability of concluding "not significant" when a discrepancy exists between Panamanians as large as that between Americans and Negroes.

§The exact Binomial is used where frequencies are small.

It seemed reasonable to draw conclusions from a detailed study of more than 10,000 cases covering a period of fifteen years. Nevertheless, it must be recognized that in disease groups with small numbers, sampling errors are large. It is important to know which difference in incidence may be accepted with confidence and which may possibly be due to sampling errors. Accordingly the data were subjected to rigorous statistical analysis. Some of the statistical evaluations are listed in Table II.

The data have been so grouped that in general two main factors are operating in the categories of Tables I and II: One economic (including dietary) and the other racial.⁶ The greatest differences in incidence occur between the

*The extent to which psychological factors may be concerned is considered in the discussion.

justify the diagnosis. Eclampsia was diagnosed in patients with no previous history of convulsion who had one or more convulsions, witnessed by a staff member, at or near term. Most of the eclampsia cases had all of the findings of the severe pre-eclampsia group in addition to their convulsions. Convulsions occurred within twenty-four hours after delivery in the cases diagnosed as post-partum eclampsia. Persistent severe albuminuria without hypertension was listed simply as albuminuria of pregnancy. Transient mild albuminuria detected in clinic was found to be very common and is discussed separately.

The maximum rise in blood pressure was determined by taking the first or second clinic blood pressure recorded, whichever was lower,* and comparing it with the highest diastolic recorded. The highest systolic blood pressure in the tabulation is in every case that accompanying the highest diastolic and is not necessarily the highest recorded. In a few cases blood pressures taken before the toxemia developed were not available and the highest diastolic blood pressure was compared with the blood pressures post partum, if these were in the normal range.

Patients were considered to have hypertension antedating their pregnancy if (a) hypertension was present on previous admissions to the hospital unassociated with a possible toxemia, or (b) hypertension was present at several successive clinic visits, the first of which occurred before the last trimester, and the hypertension persisted after delivery. Blood pressures consistently above 140/90 were considered evidence of hypertension, and in most cases these patients showed frequent blood pressures in the range of 150/100 or above. If the symptoms of their hypertension became definitely worse during the last trimester of pregnancy (usually involving a rise of 20 or more points in diastolic pressure over the previous diastolic pressure range) the patient was judged to have signs of pre-eclampsia superimposed on their initial hypertension. In most cases there was also an increase in albuminuria, edema, and subjective symptoms.

The grading and observing of edema was dependent on the judgment of the individual physician. Therefore, although its presence or absence is noted in our report, failure to find it recorded for a patient did not necessarily mean that it was never present. Similarly it was recognized that subjective symptoms were not recorded with equal care in all records. Fortunately, the blood pressure was always taken and the urine examined at each visit. Within the limits of the accuracy of their measurement, these signs could be depended upon for diagnosis and comparison. Due to contamination with the lochia, uncatheterized urine findings were not considered after delivery.

Results

Table I summarizes the main incidence data obtained. It will be seen that the Americans show a relatively low incidence of pre-eclampsia and that most of the cases are mild. While the pre-eclampsia rate for the Negro population is more than twice that for the Americans, it is no higher than the rate reported for many cities in the United States and is far below the rates cited for Trinidad and Puerto Rico. Similarly the incidence of eclampsia in Negroes, while nearly eight times the very low rate for Americans, is not unusually high by United States standards.¹ A relatively high incidence of hypertensive disease antedating pregnancy was found in the West Indian group. The superior economic status of the Panamanians on the gold pay roll was not reflected in the incidence data. Although the incidence of pre-eclampsia in this group appears to be lower than that of the silver roll Panamanians, they show the highest incidence of eclampsia.

*It was noted that the first recorded blood pressure was often considerably higher than subsequent ones, due presumably to the excitement of a first visit.

TABLE III. FETAL AND MATERNAL MORTALITY ASSOCIATED WITH TOXEMIAS

| | TOTAL CASES | NUMBER OF STILLBIRTHS AND NEONATAL DEATHS* | PER CENT | MATERNAL DEATHS | PER CENT |
|------------------------------------|----------------|--|-------------|--------------------|-------------|
| Mild pre-eclampsia | 491 | 20 | 4.1 | 0 | - |
| Severe pre-eclampsia | 146 | 28 | 19.4 | 4 | 2.7 |
| Ante- and intrapartum eclampsia | 47 | 12 | 25.5 | 10 | 21.3 |
| Postpartum eclampsia | 17 | 1 | 5.9 | 3 | 17.7 |
| Hypertension and pre- eclampsia | 66 | 8 | 12.1 | 0 | - |
| Hypertension | 60 | 8 | 13.3 | 0 | - |
| Persistent albuminuria | 36 | 2 | 5.5 | 0 | - |
| Totals | 863 | 79 | 9.2 | 17 | 2.0 |

*Includes only deaths up to approximately 1 week after delivery.

Hg ($\sigma = 9$). In the severe pre-eclamptic group it was 42 ($\sigma = 11$) and in the eclamptic patients 39 mm. of Hg ($\sigma = 12$).

It is noteworthy that in 15 per cent of the patients diagnosed as having eclampsia the highest diastolic pressure recorded was below 90 mm. of Hg compared with 2.0 per cent below this figure in the mild pre-eclampsia group and 0.7 per cent (one patient) in the severe category. It is apparent that there was a small group of eclampsia patients with definite convulsions and other symptoms, but whose blood pressure was not markedly elevated at any time that it was determined in the hospital or clinic.

In those patients with prepregnancy hypertension who developed superimposed toxemia, the average rise in diastolic pressure was 41 mm. of Hg ($\sigma = 12$) for the 18 cases considered severe, and 25 ($\sigma = 11$) for the 51 considered mild. The highest diastolic pressures averaged 133 ($\sigma = 12$) and 118 ($\sigma = 11$), respectively, in the severe and mild groups with accompanying average systolic blood pressures of 200 ($\sigma = 18$) and 180 ($\sigma = 20$).

Albuminuria.—The presence of albuminuria was noted before delivery in 93 per cent of the eclamptic and severe pre-eclamptic patients, but only 60 per cent of the mild pre-eclampsies showed this symptom. In all of these cases the urine was tested several times in the clinic and in the hospital. Cases in which the severity of the other symptoms left no doubt as to the diagnosis often failed to show albumin in the urine.

A high percentage of silver clinic patients showed albumin in their urine at some time or other during the prenatal period. During 1936 to 1940 albuminuria was found in 34 per cent of the silver clinic patients, and during 1941 to 1945 in 21 per cent.

It should be remembered in comparing figures from different clinics that the actual percentage of patients showing albuminuria in clinic is in part a function of the number of clinic visits. About 15 per cent of those visiting clinic only once during 1936 to 1945 showed albuminuria, compared with 20 per cent for those seen twice, 28 per cent after four visits, 36 per cent after six, and 45 per cent after 10 or more visits. The average number of clinic visits of all silver patients seen was 4.5.* The gold clinic incidence of transient albuminuria was strikingly lower than that of the silver clinic, averaging 9 per cent over the fifteen-year period. The techniques employed were the same, except for the fact that the gold clinic patients brought urine specimens with them in most cases.

*Many of the patients seen only once or twice proved ineligible for clinic treatment and were not followed through the remainder of their pregnancy. Thus the average number of clinic visits for patients in our main study series, all of whom delivered in the hospital, is much higher.

American and West Indian groups, and one would like to be able to attribute these differences to *either* of these two factors or to *both* in known proportions. However, the importance of economic factors can be tested only by comparing the two "Panamanian" groups. Furthermore, an insignificant result does not necessarily mean that economic factors are not important. It may mean only that the number of cases is insufficient to detect a difference. In some categories large differences in the "supply" could exist, and yet the statistical conclusion from the sample studied would be "no difference." The *liability* of making a false conclusion of "no difference" when a difference exists as large as that between Americans and West Indians is given in the last column of Table II. Similarly, racial factors can be tested only within the gold or within the silver groups, and the same precautions must be observed in interpreting the results.

In every category the Negroes had a significantly higher incidence of disease than did the Americans. Even when the gold versus silver differences are compared in Table II, they are found to be highly significant (except for eclampsia). Within the gold group, the high income Panamanians had essentially the same incidence of pre-eclampsia as the Americans, but they did have significantly more eclampsia. The Negroes have significantly more pre-eclampsia than do any of the other groups.

When the high and low income Panamanians are compared, there is no statistical basis for concluding that there is a difference in the incidence of either pre-eclampsia or eclampsia in these two groups. To conclude that there is not any difference in pre-eclampsia in these two groups is to run a 10 per cent chance of being wrong (Liability 0.1). A difference in the incidence of eclampsia as great as that between the Americans and West Indians would have been detected (Liability 0.04).

Patients With Hypertension Antedating Pregnancy.—The significantly higher incidence of hypertension in the silver patients as compared with the gold is beyond doubt. The higher incidence of hypertension in the West Indian Negroes than in the Panamanians also seems well established. Within the Panamanian groups, the incidence of hypertension in the low and high income groups could not be shown to differ significantly.

Of the 135 cases of pregnancy hypertension in which the pregnancy continued beyond the fifth month, 55 per cent showed the development of signs of superimposed pre-eclampsia. The great majority of these cases were in Negroes. Fifty per cent of the hypertensive Negroes developed pre-eclampsia, and 4 per cent had actual eclamptic convulsions. Arnell¹⁹ and Dexter and Weiss^{20, 21} report similar findings. The high incidence of abortions and stillbirths in obstetric patients with hypertension despite a good prognosis for the mother has been repeatedly emphasized.^{22-24*} This is confirmed by Table III in which it will be noted that the fetal mortality remained 12 to 13 per cent whether or not toxemia developed. There were no maternal deaths of patients with essential hypertension in this series. To the fetal deaths due to hypertension listed in Table IV must be added the 10 therapeutic abortions for hypertension noted in this series and many spontaneous abortions not recognized or recorded as associated with this condition.

Blood Pressure.—The blood pressures associated with the complications enumerated above have been analyzed and their distribution noted. The average rise in diastolic blood pressure in pre-eclampsias classified as mild was 27 mm. of

*On the contrary Sharkey and Hess²⁵ find no adverse effect of maternal essential hypertension on the child, when the incidence of abortions, premature births, stillbirths, and neonatal deaths was compared in 115 patients with essential hypertension and 2,885 without. Barnes and Browne²⁶ cite excellent evidence to show that pregnancy has no effect on the mean level of blood pressure or the incidence of hypertension at any age. They conclude that pregnancy does not cause a latent tendency to hypertension or have an adverse effect on a mother with hypertension. Furthermore, they fail to find any permanent vascular damage associated with toxemia, although the renal damage may take up to two years to heal completely. They report, however, that hypertension in the mother does increase the risk of losing the baby.

over 33 years of age. The former averaged four previous pregnancies and the latter five. However, approximately 20 per cent of the patients falling in each hypertensive category were primigravidas.

Multiple Toxemias.—Only two Americans had more than one pregnancy complicated by toxemia, one with two mild pre-eclamptic episodes and one with hypertension on the first recorded pregnancy and mild pre-eclampsia superimposed on her hypertension in the second. Two gold Panamanians had two and three mild pre-eclampsias, respectively. A third had three pregnancies with hypertension and showed definite signs of chronic nephritis with the last two of these.

In contrast, 52 of the West Indians and 13 of the silver Panamanians had a total of 150 complicated pregnancies. Ten of the West Indians and two of the Panamanians had three such pregnancies, and four of the West Indians had four. Twenty-one of the Negroes and four of the Panamanians with more than one complicated pregnancy had pre-existing hypertension with one or more of these pregnancies. Fifty per cent of these patients developed their hypertension following one or more pregnancies with mild or severe pre-eclampsia alone.

So many combinations of diagnoses on successive pregnancies were encountered in the silver group that they could not be reduced to a common table. However, it may be noted that a severe pre-eclampsia followed a mild one in eight cases, a mild succeeded a severe in eight, and pre-eclampsia superimposed on hypertension occurred after a pregnancy with hypertension alone in four. In two successive pregnancies mild pre-eclampsias were noted in 23 cases, severe ones in six, and albuminurias in four.

Fetal and Maternal Mortality.—The fetal and early neonatal mortality associated with mild pre-eclampsia was 4.1 per cent in this series, and that with severe pre-eclampsia, nearly 20 per cent (Table III). In addition, there were four maternal deaths in the latter group. While the incidence of fetal deaths was much lower in postpartum eclampsia, due to prior delivery of the child, than in ante- and intrapartum eclampsia, the difference in maternal death rate is not significant. Eclampsia accounted for more than three-fourths of the maternal deaths in the group of complications of pregnancy studied. No maternal deaths occurred among the 106 hypertensive pregnancies, although 18 of these had an apparently severe pre-eclampsia superimposed. The fetal death rate in patients with hypertension was relatively high, but was not increased when pre-eclampsia was also present.

The total incidence of stillbirths is lowest among the Americans (Table IV). The higher percentage in the gold Panamanians is probably due in part to the higher incidence of eclampsia. The over-all stillbirth incidence was 3.4 per cent. Neonatal deaths were not tabulated in the hospital records except

TABLE IV. INCIDENCE OF STILLBIRTHS IN GORGAS HOSPITAL

| | | TOTAL STILLBIRTHS FROM ALL CAUSES* | PER CENT OF TOTAL BIRTHS | STILLBIRTHS AND NEONATAL DEATHS ASSOCIATED WITH "TOXEMIA" |
|--------------------|--------------|--|--------------------------------|--|
| <i>Gold Roll</i> | Americans | 42 | 1.9 | 9 |
| | Panamanians | 25 | 2.8 | 10 |
| <i>Silver Roll</i> | Panamanians | 92 | 4.4 | 16 |
| | West Indians | 184 | 3.7 | 47 |
| <i>All Groups</i> | | 343 | 3.4 | 82 |

*Figures for total neonatal deaths were not available. During 1939 to 1941 stillbirths made up only 54 per cent of the combined total of stillbirths and neonatal deaths.

Edema.—The common occurrence of edema in pregnant women without other toxic signs has been stressed by Dexter and Weiss,²⁰ Dieckmann,¹ and others. In our series, a number of patients were hospitalized for massive edema, yet showed no albuminuria or hypertension. Nevertheless, 76 per cent of the eclamptic and severe pre-eclamptic patients, and 57 per cent of the mild pre-eclampsies were noted to show either dependent or generalized edema. However, the occurrence of mild edema may not have been recorded in some cases.

Subjective Symptoms.—The recording and interpretation of subjective symptoms, particularly of headache, was so variable that no attempt was made to analyze them. Their presence was taken into consideration in judging the classification of borderline cases.

Time of Onset.—Nearly half of the ante- and intrapartum eclampsias began in the thirty-fifth to the thirty-seventh week. Eighteen per cent of the total number began before the thirtieth week. One of the postpartum eclampsias followed a premature delivery at twenty-eight weeks, the other cases were in patients delivering at or near term.

The onset of the cases of mild pre-eclampsia showed a symmetrical distribution about a sharp peak at thirty-eight weeks. No cases occurred before the thirty-first week, and only 18 per cent of the cases occurred before the thirty-fifth week. In contrast 38 per cent of the severe cases of pre-eclampsia developed before the thirty-fifth week, and 10 per cent on or before the thirty-first week. The severe cases showed two broad peaks of onset, one at thirty-one to thirty-three weeks, and a second coinciding with the peak for mild cases around the thirty-seventh to thirty-ninth week. There was one patient whose symptoms were mild when they first appeared at forty weeks, but became severe following delivery.

The patients who developed pre-eclampsia in addition to their prepregnancy hypertension tended to do so earlier in pregnancy than the pre-eclampsia group as a whole. Furthermore, the more severe superimposed pre-eclampsias tended to begin earlier than the mild ones (average onset at 27.5 weeks, σ 5.6 as compared with 35 weeks, σ 4.5, for the mild).

While estimations of the date of onset are subject to considerable error because of the delay in seeing the physician, there seems to be a tendency in our series for the pre-eclampsias which develop earlier in the prenatal course to be more severe (cf. 26). The average onset of persistent severe albuminuria is thirty-one weeks ($\sigma = 9$) in this series, but the individual onsets range evenly from fourteen to forty-two weeks.

Age and Parity.—The many observations indicating a much higher incidence of toxemia in first pregnancies are supported by the present series. Eighty per cent of the eclampsias and 52 per cent of the pre-eclampsias were found in primiparous patients. The percentage of primiparous women seen in the silver clinic was 38 per cent. Records were not analyzed for the percentage seen in gold clinic or in the hospital.

Certain differences were noted in age incidence in the different diagnostic categories. The age incidence curve for mild pre-eclampsia followed the age distribution curve for normal pregnancies, but the severe pre-eclampsies showed two distinct incidence peaks. The first corresponded to the normal age peak for all pregnancies. The second peak occurred in the 33 to 35 year range following a period of low incidence from 27 to 29 years. The incidence of eclampsia showed this same double humped curve and differs only in the greater percentage of cases in the 14- to 23-year age range, and the somewhat later second peak (at age of 36 to 38 years). The existence of these departures from normal was confirmed by statistical tests.

The hypertensive pregnancies were symmetrically distributed about a sharp peak at the age of 30 to 32 years. Sixty-seven per cent of the hypertensives and 74 per cent of the hypertensives with superimposed pre-eclampsia were

Seasonal Incidence Changes

One of the principal points of interest in the present investigation is the influence of a tropical climate on a pathologic condition believed to fluctuate with the seasonal changes of the temperate zone. The results depicted in Fig. 1 show an apparent fluctuation in pre-eclampsia and vomiting with seasonal changes. However, this is probably deceptive and well illustrates the danger of drawing conclusions as to seasonal incidence without proper controls and statistical analysis of the data. Only the points indicated by solid circles in Fig. 1 represent significant monthly variations. The basis for calculation of significance and the actual chi square values are given in Table V. It is concluded that *no definite seasonal variation in the incidence of these toxic com-*

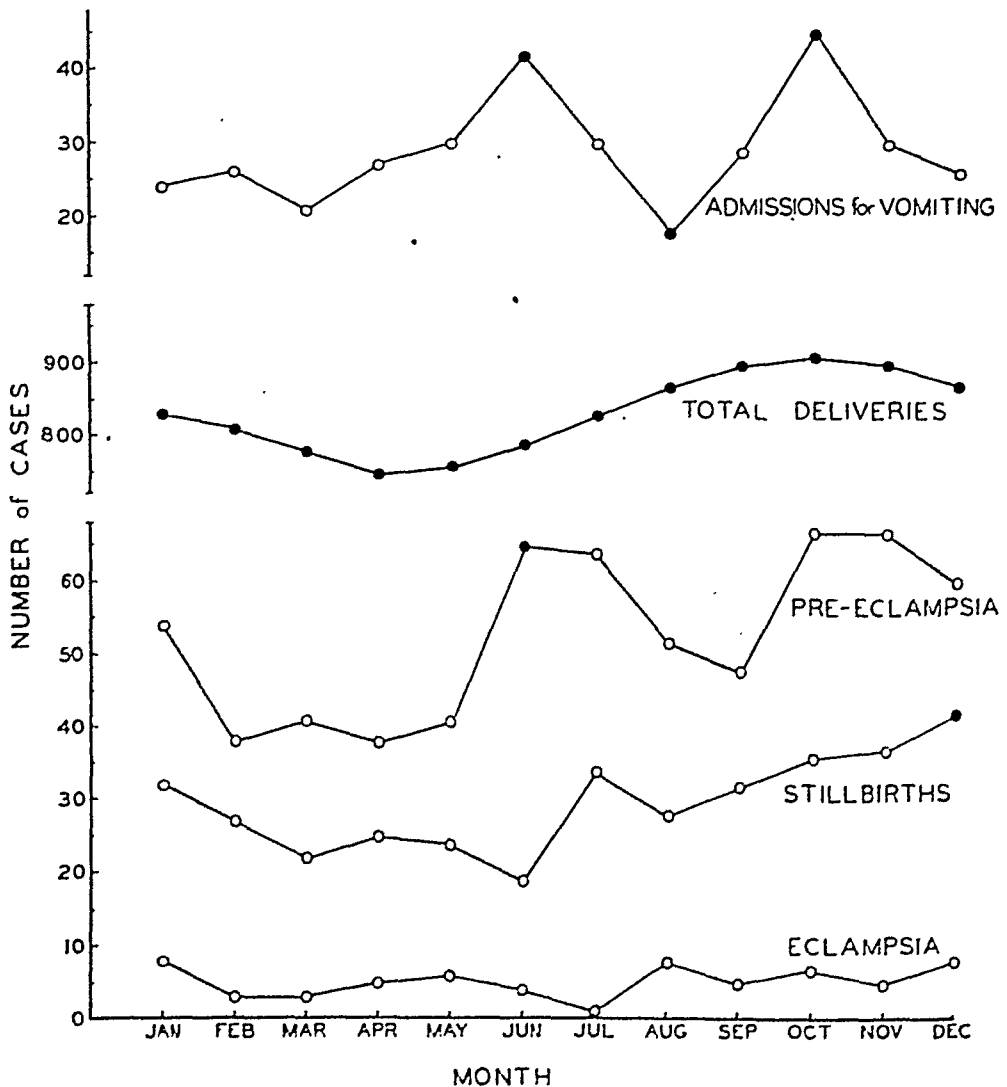


Fig. 1.—Seasonal variations in obstetric patients. The month of onset of pre-eclampsia and eclampsia and the month in which a stillbirth occurred were investigated by examining individual hospital and clinic records. The total deliveries occurring in each month from 1931 to 1945 are also plotted. The admissions for "vomiting of pregnancy" were tabulated from hospital records without verification of individual cases or correcting for repeat admissions. The seasonal variation in total births is not questioned. Those seasonal variations in incidence which are not accounted for by the seasonal variation in total pregnancies with a probability of 5 per cent or greater are represented by solid circles. The statistical data are given in Table VII.

for the years 1939 to 1941. During this three-year period there were 75 stillbirths and 63 neonatal deaths recorded. The over-all incidence of maternal deaths for the conditions investigated is 1.9 per cent of the total cases with toxic complications or 0.16 per cent of the total deliveries.

Other Complications.—Nephritis without hypertension was found in four patients, with hypertension alone in six and with pre-eclampsia alone in one. In eight cases of nephritis with hypertension, pre-eclampsia also developed and was severe in three of these. The highest incidence of nephritis occurred in the West Indian Negroes, a finding which has also been reported from autopsy studies in Panama.²⁷

In one case a severe postpartum psychosis followed eclampsia and in two cases it developed without signs of a toxemia. Two patients were admitted antepartum in an anxiety state. Ten silver and two gold patients showed signs of polyneuritis in association with previous nausea and vomiting. Pyelitis was not investigated for 1941 to 1945, but occurred in ten silver and four gold patients during the preceding ten years.

There were 251 charts signed out with a diagnosis of "vomiting of pregnancy" or "hyperemesis gravidarum." Of these, six were considered to be cases of true pernicious vomiting, three of which proved fatal. The percentage of admissions for vomiting of pregnancy which could be attributed to Americans and high income Panamanians, rose from 29 per cent in 1931 to 1940 to 59 per cent during 1941 to 1945, although their proportion of total deliveries did not change.

Of 822 abortions between 1941 and 1945, 173 were in gold and 649 in silver patients. A reliable breakdown was not readily available for the 861 abortions between 1931 and 1940.

TABLE V. SEASONAL INCIDENCE

| MONTH | CASES OF PRE- ECLAMPSIA IN 15 YR. | CORRESPOND- ING TOTAL DELIVERIES IN 15 YR. | EXPECTED CASES IN 15 YR. | PRE-ECLAMPSIA | | ECLAMPSIA | STILL- BIRTHS |
|-------|--|---|--------------------------------|-----------------------|-------------------------------|-----------|------------------|
| | F° | BASE* | F°† | (F°, F°) ^a | χ _M ^a § | | |
| | | | | FC | | | |
| Jan. | 54 | 830 | 52 | 0.1 | 0.1 | 1.8 | 0.1 |
| Feb. | 38 | 800 | 50 | 2.9 | 3.2 | 0.8 | 0.1 |
| March | 41 | 770 | 48 | 1.0 | 1.1 | 0.8 | 0.1 |
| Apr. | 38 | 770 | 48 | 2.1 | 2.3 | 0.0 | 1.3 |
| May | 41 | 780 | 49 | 1.3 | 1.4 | 0.2 | 0.1 |
| June | 65 | 810 | 51 | 3.8 | 4.2 | 0.7 | 0.4 |
| July | 64 | 850 | 53 | 2.3 | 2.5 | 3.2 | 2.4 |
| Aug. | 52 | 892 | 54 | 0.1 | 0.1 | 0.7 | 0.3 |
| Sept. | 48 | 920 | 58 | 1.7 | 1.9 | 0.2 | 0.0 |
| Oct. | 67 | 930 | 59 | 1.2 | 1.3 | 0.2 | 0.3 |
| Nov. | 67 | 920 | 58 | 1.4 | 1.5 | 0.2 | 0.8 |
| Dec. | 61 | 890 | 56 | 0.5 | 0.6 | 0.7 | 3.9 |
| Total | 636 | 10,160 | 636 | 18.4† | | | |

*Base is the total number pregnancies taken from a smoothed curve corresponding to the total number of cases of pre-eclampsia. For pre-eclampsia and eclampsia it is estimated from the total number of deliveries a month later. For stillbirths base is estimated from the total number of deliveries two weeks later. This time lag is an arbitrary but reasonable assumption. The actual time lag is not critical in the statistical analysis. The complete table for pre-eclampsia is given as an example of the method employed.

†Expected cases: $fc = \frac{\text{Base}}{10,160} \times 636$.

‡For the total test, $\chi^2 = 18.4$ with 11 degrees of freedom which has a probability, $p = 7$ per cent of a χ^2 as large or larger than the one found. The $\chi^2 = 9.5$ for eclampsia and has a probability of 60 per cent. The χ^2 for stillbirths is 10.7 and has a probability of 50 per cent. From these probabilities it is concluded that all of the seasonal variations observed in the above conditions can be accounted for by random sample variation.

§For individual months, $\chi^2 = \frac{(fo - fc)^2}{fc} (1 + 1/12)$. This correction is necessary because each month has one degree of freedom. The value of χ^2 for a probability of 5 per cent is 3.7. Only the June pre-eclampsias and the December stillbirths reach this value.

silver and gold groups. *Whatever factors made for this increase operated equally on diverse economic and racial groups.* In contrast to the pre-eclampsia rate, that for eclampsia showed sharp increases in eclampsia in 1933, 1936 and 1938. There have been no high incidence years since 1938 and the eclampsia rate has remained relatively low.

Factors of Possible Significance

The great variation in incidence of toxemia throughout the world, and even in different people in one locality, indicates that race, climate, economic status, diet, personal habits, social status, psychological stresses, and type of medical care must all be considered as factors of possible importance.

Race.—Whitacre and co-workers²⁸ compared eclampsia in Chinese in Peiping and Negroes in Memphis without observing racial differences. In New Orleans the incidence of pre-eclampsia and eclampsia has been reported to be the same in Negroes and white.^{10, 20, 30} In Panama the Negroes show a much higher incidence of the various forms of toxemia than the white Americans. If this were entirely attributal to a racial susceptibility on the part of the Negroes, then such a lowered resistance should be apparent in New Orleans. Thus it would appear that the difference in incidence of pre-eclampsia and eclampsia in this study cannot be attributed to racial factors alone.

A similar conclusion appears justified for the incidence of hypertension, although there is little doubt that the Negro in the United States has proportionately more hypertension than the whites.³¹⁻³⁷ The present study as well as reports of Thonnard-Neumann¹⁶ and Kean¹⁸ show the Negroes to have a higher hypertension rate in Panama. It might be postulated that a racial susceptibility to essential hypertension exists in the Negroes and is paralleled, under similar conditions, by a lower resistance to the transient hypertension of pre-eclampsia and eclampsia. That this is not the complete answer is indicated by the absence of hypertension in most African Negroes. These reports include the Gold Coast Colony (Odaley³⁸); Northern Rhodesia (Dry³⁸); Southern Rhodesia (Waeckford³⁸); American Zulu Mission (Taylor³⁸); Liberia (Shattuck³⁹); East Africa (Dennison^{40, 41}); Kenya (Jex-Blak⁴²); and Congo (DuBois⁴²). One must then assume the relative absence of factors precipitating hypertension in their native environment or doubt the true genetic basis for the increased hypertension in the Negro of the Western Hemisphere or both. The report that Negroes working in the city of Johannesburg, South Africa⁴² do not appear to show such a complete immunity to hypertensive cardiovascular disease is evidence for the former.

Several authors have noted a much higher incidence of hypertension¹⁶⁻¹⁸ and nephritis⁴⁴ in the West Indian Negroes as compared with the Panamanians. Yet these people appear to live under the same economic conditions and to have essentially the same diet.⁴⁵ It is not possible to conclude, however, that the differences noted between the Negroes and Panamanians in this and other studies in Panama are entirely racial. The Negroes as foreigners may be subject to greater stress in their adopted environment. *However, the fact that all Panamanians, gold and silver, seem to have somewhat less hypertension and pre-eclampsia, regardless of economic circumstances and environment, suggests that they may have some relative resistance to this condition on a genetic basis.* Whether this takes the form of a better adaptation to the climate, lower nutri-

plications of pregnancy in Panama exists in our figures for the fifteen-year period when the seasonal fluctuations in total births and the errors inherent in samples of the size studied are taken into consideration.

Annual Incidence Changes

For the two years following 1932, the incidence of pre-eclampsia remained below the figure of 4.75 per cent for this year (Fig. 2). In 1935 it rose sharply, but thereafter dropped steadily to approximately 4.5 per cent in 1938 and 1939. Since 1939 the pre-eclampsia rate has shown a continued upward trend except for a small drop in 1943. The incidence of pre-eclampsia doubled in the period from 1939 to 1945. The percentage increase was identical for both

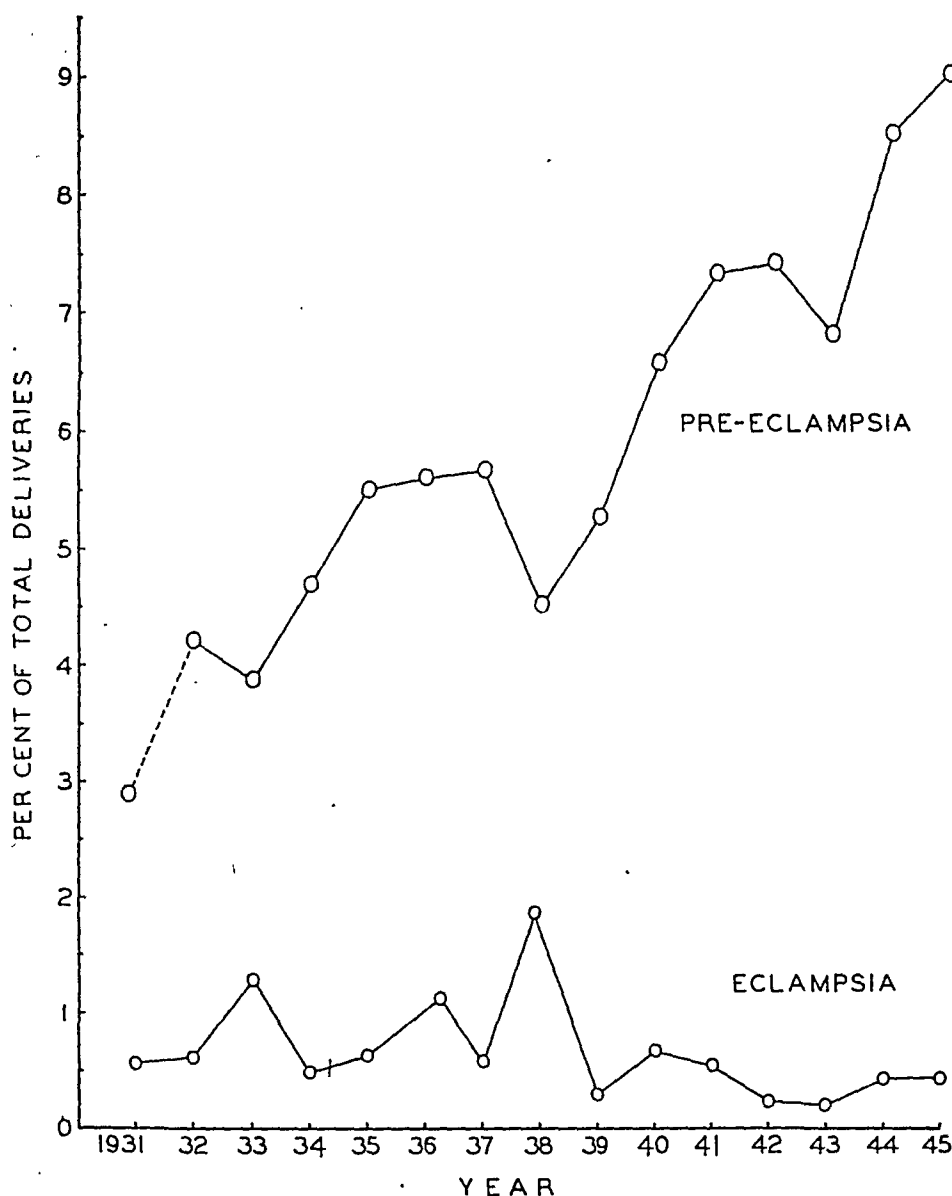


Fig. 2.—Annual incidence of pre-eclampsia and eclampsia. The value for 1931 is represented by a dotted line because the clinic records, although begun in the fall of 1930 might not be as complete for the cases delivering in early 1931 as for later years. It is hoped that the annual trends for other conditions of pregnancy can be presented in a later paper together with the inclusion of data for post-war years.

cept or satisfy either passive wishes or hostile impulses may be a provoking factor in essential hypertension.⁶¹⁻⁶⁵ It is most suggestive that the Negroes in Panama, an unassimilated and unsatisfied group confronted with greater social problems than the Panamanians, have a higher incidence of hypertensive disorders.

Gastric ulcer, another disease associated with civilization and nervous factors, has been reported to occur twice as frequently in the West Indian Negro laborer as in the native Panamanians or the Americans in the Canal Zone.^{66, 67} In contrast stands the very low incidence of peptic ulcer in Negroes in Johannesburg, South Africa hospitals.^{68, 69} The higher admission rate of Negroes in the United States to mental institutions has been attributed to the greater economic and social problems with which the Negro must struggle.⁷⁰⁻⁷² More psychosis associated with disease has been reported in the West Indian women in Panama than in any other group.⁷³

Schwab⁷⁴ has reported quantitative differences in the Negro in reaction to standard vasomotor stimuli. It is possible that the increased psychological stress incident to discrimination and to adjustment to a new situation, with or without accompanying relative racial susceptibility to neuro-vascular pathology, may have considerable influence on the incidence of both essential hypertension and pre-eclampsia in the Negroes of Panama.

Medical Care and Patient Cooperation.—Throughout the discussion it has been necessary to exclude the eclampsia rate in the gold Panamanians from the generalizations. The medical care of all the groups was essentially the same, but a few of the privileged Panamanians were decidedly uncooperative. They did not report regularly nor follow the instructions of the physician and may have unduly contributed to the small group of gold eclampsia cases. The hospital may also have accepted ineligible patients with eclampsia to the gold service through diplomatic channels when an exception would not have been made for a potential silver patient who was not entitled to Gorgas Hospital privileges. These factors cannot be evaluated a posteriori, and no conclusions as to higher incidence should be based on only 11 patients in fifteen years.

The failure of the eclampsia rate to rise during the war years as did the pre-eclampsia rate must be attributed in part to the practice of hospitalizing patients at the earliest signs of toxemia. Eclampsia was very rare in patients who reported regularly to clinic. The incidence rates given in this report do not apply to the majority of the inhabitants of Panama City, for these persons do not receive comparable prenatal care.

General Comment

Many local considerations cannot be described in detail in this report. For example, there has been considerable prejudice at times against the West Indians on the part of the Panamanians, and at one time they were refused Panamanian citizenship. On the other hand large numbers of the Negroes live in government communities within the Canal Zone where their living conditions are somewhat better than those of Panamanians and Negroes living in Panama City. The interplay of these and other local influences is hard to evaluate. In the introduction and discussion an attempt has been made to take these factors into consideration although they are not always specifically described.

The recent increase in the incidence of pre-eclampsia is of considerable interest. Since it is a proportionate increase in both gold and silver women, it would seem to reflect a response to changed conditions or cyclic influences com-

tional requirements; greater neurovascular stability, greater endocrine stability or some other constitutional difference is not known.

Diet and Economic Conditions.—Differences in incidence of toxic complications exist within the silver group between the silver Panamanians and the West Indians. However there is no evidence that sufficient differences in sanitation, living conditions, income, diet or medical care exist to account for this. Furthermore, if these factors were sufficiently important to produce differences in incidence between low income groups, they might certainly be expected to affect the high and low income Panamanian groups where differences in diet and living conditions are marked.

Nevertheless, other studies³⁻⁷ have clearly indicated the probable importance of nutrition in the incidence of "toxemias." Recently Dieckmann and associates⁴⁶ and Theobald⁴⁷ have reviewed this evidence and stressed the importance of further nutritional studies. Diet may have a relatively greater influence on the incidence of toxemia in circumstances different from those found in Gorgas Hospital patients. *We can conclude only that diet alone is not at present the limiting or determining factor in the incidence of pre-eclampsia and eclampsia in Panama. If a simple relationship between low incomes, poor diet, inferior living conditions, and a high toxemia incidence existed in Panama, there is probability of approximately 90 per cent that an analysis of our data would have indicated it.**

Climate.—The very high incidence of pre-eclampsia and eclampsia reported from Puerto Rico and Trinidad suggests that, on the basis of climate alone, the incidence of these diseases in Panama might be high. On the contrary, it is relatively low. Americans coming to the tropical climate of the Canal Zone run a lower statistical risk of "toxemia" than those in most parts of the United States. Similarly their incidence of hypertension is low. This observation is in accord with the widespread idea that circulatory stress and strain and actual hypertensive disease are less frequent and less severe in tropical climates.^{48, 55} Nevertheless, one group, the West Indian Negroes, continues to show a high incidence of hypertension in this environment. Thus a warm equitable climate alone is not sufficient to insure a low rate of hypertension, nor is it necessarily associated with a high rate of toxemia.

Although the gross monthly figures for *pre-eclampsia* incidence in this study suggest some seasonal variation, these do not reach a 5 per cent level of significance by the statistical criteria adopted. There is no evidence in our series of significant seasonal variations in *eclampsia*. Some of the many contradictory reports of correlations of eclampsia with seasonal weather changes have been cited.⁸⁻¹⁵ *It is suggested that the reason for the serious discrepancies reported in the literature is the tendency to suggest seasonal variations on admittedly inadequate data, the failure to consider seasonal variations in total deliveries, and the neglect of an adequate statistical analysis.* Sapeika⁵⁶ has recently come to similar conclusions. Jaffe's⁵⁷ idea that hypertension in Chicago Negroes is associated with the severe climatic stress of storm tracts to which they are not biologically adapted is untenable in view of the reports from Panama where the climatic stress is extremely low.⁵⁸

Psychological and Social Factors.—Hypertension is rare in Negroes in Africa but common in Negroes of the western hemisphere on a wide range of diets. Many authors have called attention to the fact that hypertension is a disease of occidental civilization.^{59, 60} There is evidence that the inability to ac-

*The experiences of Burke et al.⁵ indicate that the differences in the incidence of complications of pregnancy in excellent diet groups as compared to good and fair ones are not great. Only when the diet is poor or very poor can its adverse influence be readily detected. Although the diet of the low income patients was found to be grossly inferior to those on the higher income status of the gold payroll,⁴⁵ it is not as poor as commonly found in many clinic patients in Rochester (Scrimshaw, unpublished data) or other cities in the United States.³⁻⁵ This might account for our failure to find dietary factors of importance in this study.

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mon to both groups. The increase is a real one and not due to changed standards of medical diagnosis. No explanation of this rise is attempted at the present time, but the future trend will be followed.

Summary

The occurrence of toxic complications of pregnancy in 10,160 deliveries in Gorgas Hospital, Panama Canal Zone, in the period from 1931 to 1945 has been investigated. The incidence of pre-eclampsia, eclampsia, hypertension ante-dating pregnancy, hypertension with superimposed pre-eclampsia, albuminuria, and stillbirths is discussed in detail for the four main population groups. These include the Americans, the high income Panamanians, the low income Panamanians, and the West Indian Negroes—also a low income group. In general, the incidence of toxic complications is low in the Americans and highest in the West Indians. The annual incidence of pre-eclampsia has increased steadily since 1939. No significant seasonal variations could be found. The higher incidence in Negroes in Panama cannot be adequately accounted for by racial, dietary, therapeutic or climatic factors. It is concluded that adverse social and psychological factors affecting the Negroes to a greater degree than the other population groups may be an important influence.

The authors greatly appreciate the cooperation received from the staff of Gorgas Hospital and particularly Dr. William Coppinger, in charge of silver obstetrics and gynecology and Dr. Arthur N. Springall, assistant to the superintendent. Miss Martha Thomason greatly assisted in the tabulation of the data as did also Miss Katheryn Harrington, Dr. Robert Bays, and Dr. Roy Greer. Gratitude is also expressed to the file room staff who cheerfully located and relocated the thousands of hospital records required for this study.

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Classification

These patients were classified according to the classification prepared by the American Committee on Maternal Welfare. The distribution of the various types is set forth in Table I.

TABLE I. TYPE OF TOXEMIA

| TYPE | NUMBER | PERCENTAGE |
|----------------------------|--------|------------|
| Unclassified | 16 | 7.10 |
| Benign hypertensive | 15 | 6.70 |
| Malignant hypertensive | 9 | 4.00 |
| Chronic vascular nephritis | 1 | 0.45 |
| Acute glomerulonephritis | 1 | 0.45 |
| Chronic glomerulonephritis | 12 | 5.40 |
| Mild pre-eclampsia | 96 | 42.90 |
| Severe pre-eclampsia | 58 | 25.90 |
| Eclampsia | 16 | 7.10 |
| Total | 224 | 100.00 |

It is a simple and common-sense classification and omits conjectural and ambiguous conditions associated with pregnancy, as well as disturbances common to early pregnancy. Because of the lack of specific data to definitely classify them, 16 of our patients fell into the unclassified group. While some patients with marked tachycardia, dyspnea, hyperpyrexia, and a failure to respond to treatment are included, none was classified as eclamptic unless actual convulsions were present. Hypertensive toxemia and the various renal types were classified as such on the basis of involvement antedating the pregnancy or being present in early pregnancy, as well as on information gained in the late puerperium. One hundred seventy patients (75.9 per cent) in our series represent what we term *true* pregnancy toxemia, where the manifestations of toxemia were apparent only during the last three and one-half months of pregnancy. No cases are included where interruption of pregnancy or delivery occurred prior to six months of gestation.

The bony pelvis, as a factor governing the management of our cases, presented no problem. Table II reveals the relationship between the type of pelvis and the method of delivery.

Treatment

The object of our treatment is an attempt to return involved tissues and organs to, and to maintain them in, as nearly a physiologic capacity as possible. While we make no claim for treating any assumed cause of toxemia of pregnancy, our management of these patients is designed to treat and further prevent manifestations already demonstrated by the toxic patient. It is imperative that treatment be instituted early in order to prevent progression of seemingly insignificant findings, as well as to forestall latent sequelae. All too frequently, insouciance and procrastination in the management of novitates of a toxemic career spell latent hypertension and nephritis, as pointed out by several investigators.²⁻⁴

Many normal parturients elicit one or more signs and symptoms represented in the complex which makes up the toxemias of pregnancy. While

FURTHER OBSERVATIONS ON THE USE OF THE NEUTRAL DIET AND HYDRATION IN THE TREATMENT OF TOXEMIAS OF LATE PREGNANCY

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THE toxemias of pregnancy have long constituted a field presenting many new trends of thought and research. With current investigators constantly expanding the available data, it is not possible to condense all the information into a static picture. The literature has grown logarithmically with time, and even a bibliography on the subject would fill volumes.

Toxemia of pregnancy has always been one of the three major causes of maternal death. At present, with the advent of satisfactory sulfonamides and penicillin to combat infection, and with improved methods of collecting, storing, and administering blood and blood products, it may be safe to prophesy that pregnancy toxemia may come to rank first among the causes of maternal death.

All methods of treating the toxemias of pregnancy are designed to lower the mortality figure in this all-important death producing "disease" which is associated with or results from the pregnant state. Even though no one etiologic concept explains all the findings in pregnancy toxemia, management today resolves itself into the treatment of the signs and symptoms of a pathologic complex found only in pregnant individuals who were otherwise normal in the nonpregnant state. Regardless of the cause, the pregnancy toxemia patient presents certain manifestations which must be treated when they occur, or which must be prevented from presenting themselves at all, if possible.

Since Jan. 1, 1935, a uniform method of medical management of all patients with toxemia of pregnancy has been employed at the University of Michigan Hospital, as earlier reported.¹ All such patients have been treated according to an established conservative regime, modified to treat the individual case. In order to further evaluate this method of treatment, the records of 224 patients with pregnancy toxemia were reviewed.

The age variation was from 15 to 44 years, with 116 patients (52.2 per cent) below the age of 24 years, which is in accord with the general observation that toxemia is an affliction of young gravida. Fourteen patients (6.3 per cent) were 40 years of age or older; it is interesting to note that multiparity, hypertension, and renal disease were common to this older age group. Of the entire group of patients, 119 (53.5 per cent) were primigravidas, another observation characteristic in toxemia of pregnancy. One hundred ninety-eight patients were white; 26 (11.6 per cent) were Negroes, one of whom developed eclampsia.

TABLE II. TYPE OF PELVIS

| | TYPE OF DELIVERY | | | | | | | |
|---------------------------|------------------|-------------------------------|-----------------------|--------------|--|---|--|-----------------------|
| | NUM- BER | CESA- REAN SEC- TION | HYS- TER- OTOMY | FOR- CEPS | NOR- MAL SPON- TANE- OUS DE- LIVERY | VER- SION AND EX- TRAC- TION | DÜHR- SEN'S AND MIDFOR- CEPS | DE- STRU- CTIVE |
| Not known but parous | 8 | | 1 | 1 | 6 | | | |
| Not known but nulliparous | 7 | 1 | | | 6 | | | |
| Normal | 188 | 9 | 2 | 4 | 164 | 5 | 1 | 3 |
| Android | 13 | | | 1 | 12 | | | |
| Platypelloid | 8 | | | | 8 | | | |
| Severe contraction | 0 | | | | | | | |
| Total | 224 | 10 | 3 | 6 | 196 | 5 | 1 | 3 |
| Percentage | 100 | 4.46 | 1.34 | 2.68 | 87.5 | 2.23 | 0.44 | 1.34 |

Since we are particularly desirous that weight gain be held to a maximum of 20 pounds for the total duration of pregnancy, the average neutral diet contains approximately 2,100 calories daily. The essentials of good nutrition are not sacrificed, and the protein content maintained from 85 to 100 Gm. daily. We are not convinced that high protein intake is instrumental in producing kidney damage where no previous damage existed. Neither are we convinced that a high protein diet does anything to enhance the progress of already existing renal disease in pregnant patients.

Following is a list of foods designed to meet the daily nutritional requirements of the toxemia of pregnancy patient, supplying 2,100 calories and 85 Gm. of protein and, at the same time, furnishing a neutral ash :

- Meat or fish—1 large serving.

Eggs—3 (or 1 egg and 1 serving of meat or fish).

Bread—4 slices.

Cereal—1 serving (any cooked cereal).
Puffed wheat or rice, Quaker shredded wheat.

Rice, macaroni or spaghetti—1 serving.
- Milk—4 glasses.

Fruit—2 servings.

Vegetables.

Butter—6 pats.
- } See
List

If additional calories are needed, they can be supplied from salad oil, more bread, sugar, candy or a dessert using cereal (rice, cornstarch pudding, cake, cookies). The sodium chloride content of milk is low enough so that no significant water retention results if no more than one quart is taken daily.

Expressed in terms of meals to be provided to the patient, the above foods may be divided as follows:

| Breakfast | Lunch or Supper | Dinner |
|-------------------|------------------|--|
| Fruit (citrous) | Eggs—2 or meat | Meat or fish— |
| Cereal | or fish | 1 serving. |
| 1 Egg | Vegetable | Vegetable—1 serving |
| 2 slices of toast | Bread—1 slice | Bread—1 slice |
| 2 pats of butter | 2 pats of butter | Butter—2 pats |
| Coffee or tea | Milk—1 glass | Fruit—1 serving |
| | | Milk—1 glass |
| | | 2 glasses of milk to be taken between meals. |

many of these may be of a temporary nature, a review of the records of pregnancy toxemia patients reveals a sustained and progressive concatenation of such signs and symptoms. Likewise, the majority of severely pre-eclamptic and eclamptic patients are found, at some time during that pregnancy, to have been mildly pre-eclamptic. Too often the time interval between the initial appearance of very early signs and symptoms, without treatment, and the appearance of severe toxemia is so long that conservative treatment is of little value. It is for this reason, that attempt at control of even early symptoms and signs is advocated.

The general plan of our management of the toxemia patient is based upon the utilization of the neutral diet, ammonium chloride, abundant fluids, bed rest, sedation, and hospitalization.

Neutral Diet.—The neutral diet consists of foods which yield an equal amount of acid ash and alkaline ash, to which are added certain foods which yield an ash with no chemical reaction. These foods are prepared and served without the addition of salt and are especially selected because of their low sodium content. Bread is made without salt and sweet butter is used. The term neutral diet implies that the diet is salt free and sodium poor. It would therefore hold that foods preserved in salt such as ham, bacon, corned beef, smoked or salt water fish, pickles, and olives must be prohibited. Salt and soda form a common dentifrice and gargle and sodium bicarbonate and similar proprietary products are used for the relief of heart burn, common not only to the toxemia patient, but also frequently symptomatic in the normally pregnant individual. The diet is further characterized by a resultant ash which is neutral or slightly on the acid side.⁵ Following is a list of foods used in the diet of the pregnant patient with toxemia, indicating the type of ash yielded by each.

FOODS WHICH YIELD

| <i>An Acid Ash:</i> | <i>A Neutral Ash (or none):</i> | <i>A Basic Ash:</i> |
|-------------------------------|---|---|
| Meat | Butter | Milk |
| Fish | Cooking fats | Cheese |
| Eggs | Salad oils | Vegetables |
| Cereals and their products | Sugar | Fruits (with the exceptions under "acid") |
| Breakfast cereals | Tapioca | Beans (lima kidney) |
| Bread | Gelatine | Almonds |
| Rice | Vinegar | Chestnuts |
| Macaroni | Cornstarch | |
| Spaghetti | Tea | |
| Hominy | Coffee | |
| Corn | | |
| Lentels | | |
| Peanuts | | |
| Walnuts | | |
| Prunes | containing benzoic acid which is con- jugated with glycine and excreted as hip- puric acid. | |
| Plums | | |
| Cranberries | | |

preserve the normal functioning capacity of the kidney instead of producing overtaxation of the physiologic renal unit. When intravenous fluids are administered, 5 per cent glucose in distilled water is given in order to avoid the attendant increased water retention accompanying the administration of glucose in saline or Ringer's solution. Likewise sodium bicarbonate or similar preparations are not given. Hypertonic solutions of glucose are not used since they must be converted to isotonic solutions by the liver in effecting normal water metabolism.

It is generally thought that forcing fluids in the toxemia patient will increase edema. This is true only when sodium bicarbonate or uncontrolled sodium chloride ingestion is permitted. In an experience with a few patients in this series, it was found that with drinking 8,000 to 9,000 c.c. of water daily, plus the other measures of therapy outlined here, there was no increase in edema, blood pressure, albuminuria, or weight gain. On the other hand, a small group of controlled patients were given large amounts of water with large amounts of salt and soda; this was followed by a sharp increase in weight gain, demonstrable edema and a significant rise in blood pressure. These patients were not continued on the high sodium intake to determine whether increased albuminuria would occur. All signs and symptoms disappeared after ammonium chloride, neutral diet, and forced fluids were resumed.

Ammonium Chloride.—Ammonium chloride is administered to release the sodium ion from the tissues and to release the intercellular fluid retained by the sodium. It is given in 0.5 Gm. gelatin capsules in order to insure complete absorption. Ammonium chloride in phenyl salicylate coated tablets has, in our experience, usually resulted in producing little or none of the desired effect, and, furthermore, the tablets have frequently been recovered unchanged in the stool. The capsules are given *with* the meals in order to reduce nausea and vomiting. The average dose is 3.0 Gm. (45 grains) three times daily and is continued for four days. To patients in coma or with convulsions, ammonium chloride may be administered through a stomach tube after convulsions have been controlled. The ammonium chloride is given in a 20 Gm. (300 grains) dose mixed with 250 c.c. of 40 per cent cream in order to limit gastric irritation. Also in this type of patient, ammonium chloride may be given intravenously (0.9 per cent solution in 1,000 c.c. 5 per cent glucose) with satisfactory response. The ammonium chloride breaks down in the gastro-intestinal tract and is absorbed as ammonium and chloride ion. After reaching the liver, the ammonium ion combines with CO_2 and H_2O to form ammonium carbonate which is converted to urea. The urea is excreted in the urine as such. The chloride ion combines with the sodium of the carbon-dioxide combining power of the blood in the extracellular spaces and is excreted through the kidneys as NaCl in water. The acid-base diagram, originally proposed by Gamble,¹³ reveals an increased chloride concentration and a decrease in base bicarbonate. Since the kidney tends to reconvert urea to ammonium ion after prolonged ammonium chloride administration, ammonium chloride is therefore excreted as such. For this reason, ammonium chloride administration is not continued for periods longer than four days at a time. Its ingestion is then resumed after a rest period of three days. During these periods of administration a moderate inorganic acidosis is induced, but rarely does the CO_2 combining power fall below 45 volumes per cent if interrupted therapy is practiced.

Because the tissues of most severe toxemia patients are filled with water, due to the extracellular presence of enough sodium to retain water, the blood vascular system is usually dehydrated. Thus little of the retained fluid content of the body is made available to the circulating blood and to the kidneys. Since dehydration and oliguria are usually constant features of the severely toxic patient, an effort is made to combat this dehydration and to make water

An excessive weight gain in pregnancy toxemia patients, due to overeating, is more often the rule rather than the exception. In these overweight patients a neutral diet containing 1,400 to 1,500 calories may be secured by substituting skimmed for whole milk, using three teaspoons of butter, and by using fresh fruits or those canned without sugar.

Only the following fruits and vegetables are used:

| | | |
|------------------------------|-------------------------------|------------------------------|
| <i>3 Per Cent Vegetables</i> | <i>6 Per Cent Fruits</i> | <i>9 Per Cent Fruits</i> |
| Asparagus | Cantaloupe | Grapefruit |
| Cabbage | Watermelon | Grapefruit juice |
| Cauliflower | | |
| Lettuce | <i>6 Per Cent Vegetables</i> | <i>9 Per Cent Vegetables</i> |
| Mushrooms | Pumpkin | Beets |
| Radishes | Squash | Carrots |
| Tomatoes | String beans | Onions |
| Tomato juice | Turnips | Rutabagas |
| Celery | | |
| Cucumber | <i>15 Per Cent Fruit</i> | |
| | Apples | |
| <i>12 Per Cent Fruit</i> | Grapes | |
| Apricots | Pears | |
| Cherries | | |
| Oranges | <i>15 Per Cent Vegetables</i> | |
| Orange juice | Parsnips | |
| Pineapple | Peas | |
| Raspberry juice | | |

Fluids.—While therapeutic recommendations of the amount of water necessary to treat the pregnancy toxemia patient have varied from one extreme to the other, there can be no debate that sufficient water is required to carry off such products of metabolism as the kidneys ordinarily excrete. Some ambiguity in the meaning of water balance seems to exist. We do not feel, as does Arnold,⁶ that a patient is in water balance when ingested fluid equals the amount of water excreted as urine. As has been shown by Newburgh and his associates, normal water balance takes into account water excreted through the kidneys, skin, expired air, and stool. With established figures available on what water balance is in the normal nonpregnant⁷⁻¹¹ and in the normally pregnant¹² individual for a 24-hour period, our treatment is, in part, based on replacing fluids in such amounts as to insure the requirements for normal water metabolism. We have developed a definite "fluid consciousness" in the treatment of the toxemias of pregnancy. Fluids are forced to a level sufficiently high to produce urinary excretion approximately equal to the output of a normal individual. When the fluid intake reaches such a level, the requirements for water of expired air, perspiration, and water of stool are also satisfactorily supplied. Since the majority of our severely toxic patients show both clinical and laboratory evidence of dehydration, the first attempts in our management of these patients are designed to correct this dehydration and to approximate normal renal function as nearly as possible.

Fluids are supplied by mouth, parenterally, or by both routes, if necessary, in order to insure a minimum daily urinary output of 2,000 cubic centimeters. Frequently a daily minimum fluid intake of 4,000 cubic centimeters is necessary to effect the result of normal water balance. We wish to emphasize that inundation is not only impractical but unnecessary and fatuous. Since normal renal function signifies the excretion of waste products and solids in water, we feel that excretion of these products in large amounts of urine tends to

TABLE III. FUNDUSCOPIC FINDINGS

| | NUM- BER CASES | PER CENT | UNCLAS- SIFIED | BENIGN H.B.P. | MALIGNANT H.B.P. | CHRONIC VASCU- LAR NE- PHRITIS | ACUTE GLOMER- ULONE- PHRITIS | CHRONIC GLOMER- ULONE- PHRITIS | MILD PRE- ECLAMP- | | SEVERE PRE- ECLAMP- | |
|--|----------------------|-------------|-------------------|------------------|---------------------|---|---------------------------------------|---|-------------------------|---------|---------------------------|---------|
| | | | | | | | | | SIA | ECLAMP- | SIA | ECLAMP- |
| Normal | 60 | 48 | 1 | 4 | -- | 1 | 1 | 6 | 26 | 16 | 5 | 5 |
| Generalized vascular disease, with or without spasm | 38 | 30 | -- | 3 | -- | -- | -- | 4 | 13 | 14 | 4 | 4 |
| Hypertensive neuroretinitis | 19 | 15 | -- | -- | 4 | -- | -- | -- | 3 | 8 | 4 | 4 |
| Hypertensive neuroretinitis with hemorrhages, exudates, or both | 8 | 7 | -- | -- | 3 | -- | -- | 2 | -- | 2 | 1 | 1 |
| Total | 125 | 100 | 1 | 7 | 7 | 1 | 1 | 12 | 42 | 40 | 14 | 14 |

available to the kidneys. With this increased fluid intake and a lowered sodium intake, more water is made available for its diuretic effect and for normal water metabolism. Ammonium chloride, in releasing extracellular water, further renders stored water available. In this manner, the extracellular spaces are dehydrated to normal and the blood vascular system hydrated, thus delivering additional water for urinary excretion of solids and waste products.

Sedation.—In the majority of cases little sedation is required, particularly in mild pre-eclampsia. Phenobarbital in doses of $\frac{1}{2}$ to $\frac{3}{4}$ grain four times daily usually suffices. However in the severely toxic patient sodium phenobarbital given intramuscularly in 5 grain doses every five hours has proved a most satisfactory sedative. In toxemia with convulsions, we formerly favored the use of avertin in about one-half the basal anesthetic dosage. With a 50 mg. per kilogram dosage we encountered no patient whose convulsions were not promptly controlled. No manifestations of liver damage from avertin were noted. Because of the time required for preparation of the avertin and the consequent delay in controlling convulsions we no longer use avertin except in the occasional case. Instead, convulsions are brought under control by intravenous use of pentothal sodium 0.162 mg. This is repeated if necessary. After control of the convulsions, patients are satisfactorily and deeply sedated with intramuscular sodium phenobarbital (usually thirty-six to forty-eight hours) while medical measures of treatment of the toxemia are instituted and continued. When these patients reveal evidence of response to medical management, sedation is gradually diminished until consciousness is attained. Since the control of convulsions is not synonymous with the control of eclampsia, the patient is continued on treatment as a pre-eclamptic with the neutral diet, abundant fluids, ammonium chloride and a sedative dosage of barbiturates by mouth. Magnesium sulfate was seldom used. The experimental utilization of veratrum viride in eight of our patients did not encourage its continued use.

Hospitalization.—In the presence of early signs and symptoms of a mild toxemia, patients are instructed on a neutral type of diet and given instruction on care at home. They are seen every third day in the clinic for checkup, but since the majority of these patients fail to improve at home, we feel that all early toxemia patients should have a short period of inculcation in home care during a preliminary period of hospitalization. All other types of toxemias are immediately hospitalized for complete care.

Special Measures.—Phlebotomy was performed in three of our cases, all of whom were severely toxic. In each instance there was evidence of left ventricular failure with pulmonary edema. Five hundred to seven hundred cubic centimeters of very concentrated blood the consistency of catsup were removed with resultant dramatic improvement. At the same time, intravenous 5 per cent glucose was slowly administered. None of the patients thus treated died. Oxygen therapy was used freely in the majority of our eclamptic or severely pre-eclamptic patients or where there was any evidence of cyanosis or dyspnea. Digitalis in one-half the digitalization dose was used in those with heart failure. None of the patients presented valvular heart disease.

The ocular fundus was investigated in 125 of our patients and the results recorded in Table III. Those patients showing ophthalmoscopic evidence of involvement and those showing no evidence of abnormal findings were about equally distributed.

Malignant hypertensive disease revealed significant retinal damage in 100 per cent of those examined. Unless vascular sclerosis was also present, patients were not classified in this group of toxemias.

Significant funduscopic findings were noted in over 50 per cent of the patients examined in almost every type of toxemia. Two patients were com-

Induction of Labor

The treatment of pregnancy toxemia embodies two general types of management: (1) medical, and (2) termination of pregnancy. In general the former treats the disease process complicating the pregnancy, while the latter treats the pregnancy. Many of the methods of interrupting a toxemic pregnancy have stressed the surgical rather than the obstetric approach. Such surgical intervention has accounted for many of the deaths ascribed to the toxemia. Termination of pregnancy, in our clinic, is now considered an *adjunct* to already established medical treatment only when such established treatment has failed to control the toxemia. When induction of labor is indicated, medical induction and/or rupture of the membranes are preferred and normal spontaneous delivery (including low forceps) the favored method of delivering these patients.

TABLE V. INDUCTION OF LABOR

| | NUM- BER | SPONTA- NEOUS | MEDI- CAL | RUPTURE OF MEM- BRANES | INTRA- OVULAR BAG | CESA- REAN SECTION | HYSTER- OTOMY |
|----------------------------|-------------|------------------|--------------|------------------------------|-------------------------|--------------------------|------------------|
| Unclassified | 16 | 11 | 4 | 1 | | | |
| Benign hypertensive | 15 | 12 | 3 | | | | |
| Malignant hypertensive | 9 | 5 | | 2 | | | 2 |
| Chronic vascular nephritis | 1 | | | 1 | | | |
| Acute glomerulo | 1 | | | | | | 1 |
| Chronic glomerulo | 12 | 8 | 3 | | 1 | | |
| Mild pre-eclampsia | 96 | 64 | 21 | 5 | 2 | 4 | |
| Severe pre-eclampsia | 58 | 36 | 12 | 3 | 3 | 4 | |
| Eclampsia | 16 | 6 | 1 | 4 | 3 | 2 | |
| Total | 224 | 142 | 44 | 16 | 9 | 10 | 3 |

There are those who advocate immediate termination of pregnancy where the following conditions prevail: (1) in the presence of convulsions; (2) if convulsions are believed to be inevitable; (3) if the medical regime appears to be endangering the patient's renal or ocular status; and (4) where no improvement occurred under medical treatment. For the most part, we favor interruption in 100 per cent of those showing no improvement under medical management. We believe that the first two situations are conditions requiring medical management until such time as these conditions are controlled or do not improve. As previously stated, funduscope response to treatment does not keep pace with clinical response.

Cesarean Section

Cesarean section, as a satisfactory method of delivering the toxemia of pregnancy patient, presents subject material for endless debate. The proponents of cesarean section argue in terms of lowered maternal mortality. While there was no maternal mortality among our sectioned toxic patients, we are not prepared to advocate its use in the management of toxemia of pregnancy. On the basis of our and others' data, we feel that extra-toxemic factors should determine the indications for cesarean section. The cesarean operation was performed in 10 patients, an incidence of 4.5 per cent, and factors pertinent to these cases are set forth in Table VI.

Pelvic obstruction presented no indication for section except in one eclamptic primipara with such massive edema of the vulva as to preclude delivery by any other method. Previous cesarean section presented an indication for repeat section in three instances, one of which presented another real indication, total placenta previa. Abruptio placentae, diabetes and obstructive edema furnished the indications for celiotomy in one each. Since

pletely amaurotic due to massive postretinal edema producing retinal detachment; under therapy the edema completely cleared and vision subsequently returned to normal. In evaluating the status of the ocular fundi as an indication for determining interruption of pregnancy or the efficacy of medical therapy, we have noted that the eye ground status does not tend to clear with the same rapidity as do the other manifestations of toxemia. For this reason, the persistence of retinal changes, in the presence of other clinical improvement, has led us to rely upon general clinical response rather than upon the ophthalmologist in determining the advisability of termination of pregnancy.

Response to Treatment

The majority of the patients responded favorably to our method of medical management as illustrated in Table IV.

TABLE IV. RESPONSE TO TREATMENT

| TYPE OF TOXEMIA | | NUM- BER | NO TREAT- MENT | IM- PROVED | NO CHANGE | PRO- GRES- SIVE | MATER- NAL MOR- TALITY |
|----------------------------|----------|-------------|----------------------|---------------|--------------|-----------------------|------------------------------|
| Unclassified | | 16 | 1 | 9 | 6 | -- | 0 |
| Benign hypertensive | | 15 | -- | 12 | 3 | -- | 0 |
| Malignant hypertensive | | 9 | 2 | 1 | 3 | 3 | 3 |
| Chronic vascular nephritis | | 1 | -- | 1 | -- | -- | 0 |
| Acute glomerulonephritis | | 1 | -- | 1 | -- | -- | 0 |
| Chronic glomerulonephritis | | 12 | 2 | 7 | 2 | 1 | 0 |
| Mild pre-eclampsia | | 96 | 3 | 80 | 10 | 3 | 0 |
| Severe pre-eclampsia | | 58 | 1 | 44 | 11 | 2 | 2 |
| Eclampsia | | 16 | | 14 | 2 | -- | 1 |
| Total | Number | 224 | 9 | 169 | 37 | 9 | 6 |
| | Per cent | 100 | 4.01 | 75.4 | 16.5 | 4.01 | 2.67 |

While one malignant hypertensive exhibited evidence of improvement, the remainder of those treated showed no change in status or revealed definite progression of signs and symptoms. No improvement was anticipated in this group and since none resulted, we feel that these patients have nothing to gain by permitting the pregnancy to advance to the last trimester. Among those patients presenting no change or progressive signs of toxemia, the majority were in an extreme state of toxemia.

More than 80 per cent of the patients with so-called "true" toxemia of pregnancy (mild and severe pre-eclampsia and eclampsia) responded to our medical management. Especially well did the eclampsia group respond to medical treatment, and only one of these died.

Favorable response to treatment occurs within forty-eight hours after institution of treatment and patients usually continue to maintain a favorable course. Patients thus responding are kept on a conservative regimen until labor intervenes or, after sustained improvement at term, until labor is induced. If, after five to seven days of conservative treatment, there is no satisfactory response to treatment, we feel that termination of pregnancy by the most conservative means for that patient is indicated. We do not feel that indiscriminate termination of pregnancy is indicated just because a patient with an untreated toxemia has reached an arbitrary number of weeks of pregnancy.

Simrall,¹⁴ in a follow-up study of 100 patients treated by this method, found no evidence of significant vascular or renal morbidity in patients known to be normal prior to their toxemic pregnancies.

TABLE VII. ECLAMPSIA

| NO. | CASE NO. | PARA | TIME INTERVAL BETWEEN FIRST ANTEPARTUM VISIT AND DELIVERY | DURATION OF TOXEMIA TREATMENT BETWEEN ECLAMPSIA AND DELIVERY | WEIGHT GAINED DURING PREGNANCY | DURATION OF PREGNANCY | INDUCTION OF LABOR | TYPE OF DELIVERY |
|-----|----------|------|---|--|--------------------------------|-----------------------|--------------------|------------------|
| 1 | 353293 | 0 | 6 months | 15 minutes | 25 pounds in 6 mo. | 9 mo. | Spontaneous | Low forceps |
| 2 | 361549 | 0 | 1 month | 5 minutes | Not known | 9 mo. | Spontaneous | Normal |
| 3 | 367931 | 12 | None | 2 hours 15 minutes | Not known | 8½ mo. | Spontaneous | High forceps |
| 4 | 372917 | 0 | None | Delivered elsewhere | -- | 9 mo. | Spontaneous | Normal |
| 5 | 380416 | 0 | 5 months | 2 days | 47 pounds in 5 mo. | 8½ mo. | Bag | Destructive |
| 6 | 392652 | 0 | 3 months | None | 14 pounds in 3 mo. | 9 mo. | -- | Section |
| 7 | 393394 | 0 | None | 2 days | Not known | 8 mo. | Ruptured memb. | Low forceps |
| 8 | 394637 | 0 | None | 3 hours | 23 pounds | 7½ mo. | Spontaneous | Normal |
| 9 | 395757 | 0 | None | 11 hours 15 minutes | 25 pounds in 3 mo. | 8½ mo. | Medical | Normal |
| 10 | 407383 | 0 | 6 weeks | None | 10 pounds in 6 wk. | 8½ mo. | Medical | Normal |
| 11 | 412703 | 3 | None | Delivered elsewhere | -- | 9 mo. | Spontaneous | Normal |
| 12 | 438816 | 0 | None | 12 hours | Not known | 9 mo. | Bag | Midforceps |
| 13 | 444374 | 0 | None | 12 hours 15 minutes | Not known | 6 mo. | Bag | Normal |
| 14* | 451428 | 8 | None | 15 hours 10 minutes | Not known | 7½ mo. | Spontaneous | Normal |
| 15 | 456120 | 0 | None | 33 hours 25 minutes | Not known | 7 mo. | Spontaneous | Normal |
| 16 | 484786 | 0 | None | 48 hours | Not known | 8½ mo. | -- | Section |

*Maternal Death.

81.3% Primiparas.

Nine patients developed toxemia convulsions at or earlier than eight and one-half months of gestation, while only two artificial inductions were performed in patients whose pregnancy had advanced to less than eight and one-half months. Cesarean section was performed in two patients, one for soft tissue obstruction, the other for eclampsia itself.

Eclamptic patients, in our clinic, are generally managed conservatively. We feel that these patients should be given a trial of medical therapy to determine the ability to respond. If no improvement in status occurs or if symptoms and signs are progressive, we favor termination of pregnancy in the most conservative manner for that patient. As previously noted, patients with convulsions or coma are not fed for three days in order to develop a mild starvation acidosis. Convulsions are controlled by intravenous pentothal sodium and deep sedation maintained by intramuscular sodium luminal (5 grains every five hours) for the next forty-eight hours. Immediately after control of convulsions, crystalline ammonium chloride is administered by stomach tube, and 5 per cent glucose in water given intravenously to maintain a total 24-hour minimum intake of 4,000 cubic centimeters. When blood pressure, edema, and albuminuria subside, sedation is gradually decreased until food and fluids can be taken by mouth. The patient is then placed on the regimen for pre-eclampsia and thus maintained until delivery occurs or until failure of improvement indicates termination of pregnancy. Frequently during the first three days of treatment, the patient may void as much as 7,000 to 8,000 c.c. of urine per 24-hour period, with great loss of edema. Not uncommonly such diuresis is accompanied by a drop in albuminuria from four plus, to a trace, or none.

Mortality

Mortality figures are usually proportionate to the length of antepartum observation time, where keenness of the physician and cooperation of the patient simultaneously operate. Six of our patients died with, but not necessarily from, toxemia as noted in Table VIII.

TABLE VI. CESAREAN SECTIONS

| YEAR | PARA | TYPE OF PELVIS | INDICATION FOR SECTION | TYPE OF TOXEMIA | DURATION OF PREGNANCY | DURATION OF TREATMENT PRIOR TO SECTION | REMARKS |
|------|------|----------------|--|----------------------|-----------------------|---|-------------------------------------|
| 1936 | 2 | Normal | Previous section | Mild pre-eclampsia | Term | 2 days | |
| 1937 | 0 | Normal | Eclampsia | Eclampsia | Term | Sectioned on admittance date | |
| 1937 | 0 | Normal | Severe pre-eclampsia | Severe pre-eclampsia | Term | 1 day | |
| 1939 | 5 | Normal | Total placenta previa | Severe pre-eclampsia | Term | 18 days—then developed signs of Pl. Pr. | Previous section |
| 1939 | 0 | Normal | Pre-eclampsia—failed to respond to treatment | Severe pre-eclampsia | Term | 14 days (failure) | Primipara breech |
| 1939 | 1 | Normal | Diabetes and mild pre-eclampsia | Mild pre-eclampsia | 8½ mo. | 6 days | Section done to prevent still-birth |
| 1941 | 0 | Normal | Mild pre-eclampsia | Mild pre-eclampsia | Term | Sectioned on admittance date | |
| 1941 | 0 | Not examined | Marked vulvar edema and eclampsia | Eclampsia | 8½ mo. | 2 days | Admitted in eclampsia |
| 1941 | 3 | Normal | Previous section | Mild pre-eclampsia | Term | 1 day | |
| 1943 | 1 | Normal | Severe abruptio placentae | Severe pre-eclampsia | 8½ mo. | Sectioned on admittance date | Dead fetus; hysterectomy performed |

sectioning the diabetic patient with a mild pre-eclampsia at eight and one-half months of gestation, we have modified our former idea of delivering these patients by section.

Toxemia of pregnancy itself was considered an indication for cesarean section in four patients. Even though this method of delivery was used in these patients, we, again, do not feel prepared to recommend cesarean section for the treatment of toxemia. Although these patients were primiparas, we consider, on hind sight, that three of these four patients might well have been allowed to deliver normally after medical induction of labor. Failure to respond to treatment and a breech presentation in a primipara may constitute valid indications. Among these four patients sectioned because of their toxemia, it is probable that they could have been given a longer trial on medical management before delivery. These patients were sectioned during the first thirty-six hours of hospitalization without an adequate trial of medical management. We no longer subscribe to sectioning the eclamptic patient until a sufficiently adequate trial of medical therapy has determined the value or futility of such treatment. On the basis of our review, we feel that no hard and fast rules can be proposed regarding section except that we do not feel that uncontrolled eclamptics should be sectioned.

Eclampsia

Toxemia with convulsions occurred in 16 of our patients, an incidence of 7.1 per cent. No patient, even though in coma, was classified as eclamptic unless actual convulsions were or had been present. That eclampsia is an affliction of primiparas (81.3 per cent) is noted in Table VII. Only a small group of these eclamptic patients (18.7 per cent) received what might be interpreted as a beginning of prenatal care, varying from three to six months prior to delivery. The remainder received little or no care. Incomplete data on weight gain during pregnancy precludes any statement regarding any relationship to the development of eclampsia.

2. Toxemias of pregnancy are treated according to a conservative regimen, consisting of hydration, neutral diet, ammonium chloride, bed rest, and mild sedation.

3. Conservative therapy of pregnancy toxemia embodies the modern principles of water balance.

4. When conservative methods fail to control pregnancy toxemia, termination of pregnancy is effected by the most conservative means suited to the particular individual.

5. The latent sequelae following pregnancy toxemia are minimized by such conservative therapy.

6. The indications for cesarean section in toxemia patients should be essentially the same as when no toxemia exists.

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TABLE VIII. MATERNAL MORTALITY

| AD-MITTED | DIED | DURATION OF ANTE-PARTUM TREATMENT IN CLINIC | DURATION OF HOSPITAL TREATMENT | TOTAL TIME DURATION OF HOSPITALIZATION | TYPE OF DELIVERY | DURATION OF PREGNANCY | CAUSE OF DEATH | TYPE OF TOXEMIA |
|------------------------|-----------------------|---|---|--|---------------------|-----------------------|------------------------|------------------------|
| 5:00 P.M. 3/28/35 | 7:45 P.M. 4/16/35 | None | 2 hours 45 minutes (ante-partum) 19 days (post-partum) | 19 days plus 2 hours 45 minutes | Low forceps | 8 months | Pulmonary tuberculosis | Severe pre-eclampsia |
| 2:15 P.M. 5/ 4/35 | 4:30 P.M. 5/ 4/35 | None | None | 2 hours 15 minutes | Undelivered | 7½ months | Cerebral hemorrhage | Malignant hypertensive |
| 11:00 A.M. 11/12/37 | 3:40 P.M. 11/14/37 | None | 24 hours (ante-partum) | 52 hours 40 minutes | Vaginal hysterotomy | 6 months | Cerebral hemorrhage | Malignant hypertensive |
| 10:15 A.M. 7/ 6/38 | 2:00 P.M. 7/ 6/38 | None | None | 3 hours 45 minutes | Low forceps | 8 months | Atelectasis | Severe pre-eclampsia |
| 11:30 A.M. 10/15/39 | 6:00 P.M. 10/16/39 | None | 21 hours (ante-partum) 9 hours 30 minutes (post-partum) | 30 hours 30 minutes | Normal | 7½ months | Pulmonary edema | Eclampsia |
| 5:45 P.M. 9/20/40 | 6:00 P.M. 9/23/40 | 2 months (totally unco-op) | 6 hours (ante-partum) 48 hours (post-partum) | 54 hours | Normal | 7½ months | Coma | Malignant hypertensive |

The over-all maternal mortality rate was 2.67 per cent, while the malignant hypertensive group accounted for 50 per cent of the total mortality. The mortality rate in eclampsia was 6.25 per cent, while the rate due to pre-eclampsia was 1.3 per cent. We feel that most of the deaths were preventable, since the problem of maternal mortality control seems to be confined to a period considerably earlier than the time of appearance of the death-dealing factor. While the malignant hypertensive group presented evidence of disease early in pregnancy, which had already spelt their doom, we are able to state that pregnancy precipitated the gravity of this existing disease and was, in a large measure, the major factor in shortening life. Since the paramount object of good prenatal care is to reduce maternal mortality to zero, so must therapy consider lengthening life by rendering the change found in toxemia as ephemeral as possible. Such prenatal care must necessarily include a sten-torian stand on interruption of pregnancy at the earliest sign of continued damage in spite of instituted remedial measures. In such patients where artificial termination is justified in the hypertensive and nephritic groups, permanent sterilization at the same time is also equally justified if we are to preserve an enviable record in diminishing this important cause of maternal death.

The gross fetal mortality was 14.2 per cent; the cause of death in the majority of instances was prematurity, while monstrosities accounted for four deaths.

Summary

1. Patients with toxemias of late pregnancy are generally managed conservatively.

The amount of mucus available for analysis at midcycle ranged from approximately 100 to 400 milligrams. At other times in the cycle, i.e., in the pre- and postovulatory phases, the amount of mucus obtained was greatly reduced, 15 to 50 milligrams being representative. Specimens weighing less than 10 milligrams did not lend themselves to analysis.

Water Content.—The water content of the mucus was determined by drying specimens to constant weight in an oven at 55° C.

Measurement of Reducing Substances.—The Shaffer-Hartman copper reagent as modified by Somogyi¹⁶ was used throughout these studies. By using this reagent it is possible to determine quantitatively very small amounts of reducing substance since the cuprous oxide formed is not easily reoxidized. Furthermore, this reagent is not as readily reduced by substances other than glucose as are some of the other reagents in common use.

The heating period with 2 c.c. of the copper reagent added to the samples was twenty minutes in a boiling water bath. After acidification with 3 c.c. of 1 N sulfuric acid, the usual iodometric titration was carried out with sodium thiosulfate. A standard glucose curve was determined, and all the results were expressed as milligrams per cent glucose.

1. *Free reducing substance:* The copper reagent was added to a weighed quantity of mucus and the amount of reducing substance determined as outlined above.

2. *Total reducing substance:* A weighed amount of mucus was hydrolyzed in 2 c.c. of 1 N sulfuric acid for three hours in a boiling water bath. The solution was then neutralized with 2 N sodium hydroxide, using phenolphthalein as the indicator. The copper reagent was then added and the amount of reducing substance determined.

3. *Per cent fermentable reducing substance:* Hydrolysis of the mucus specimen was carried out as in the determination of total reducing substance. After neutralization with the sodium hydroxide the volume was brought to 10 c.c. A 4 c.c. aliquot was used for the determination of total reducing substance. A 5 c.c. aliquot was fermented for fifteen minutes at approximately 37° C. with yeast.* After centrifuging, 4 c.c. of the supernatant were used to determine the amount of reducing substance remaining. The difference between the reducing substance values before and after fermentation gave the amount of fermentable material, presumably glucose.

4. *Free reducing substance in precipitate:* A known amount of cervical mucus was digested with 1 c.c. of 30 per cent potassium hydroxide, 3 c.c. of 95 per cent alcohol were added, and the tubes were then allowed to stand overnight in the refrigerator. This is a standard procedure for the precipitation of glycogen. After centrifuging, the supernatant was decanted for separate analysis.

The precipitate was dissolved in 1 c.c. of distilled water, the copper reagent was added, and the amount of reducing substance determined.

5. *Free reducing substance in supernatant:* The alcohol in the supernatant obtained by the precipitation method described above was evaporated off in a boiling water bath. The solution was then neutralized with sulfuric acid, the copper reagent was added, and the amount of reducing substance determined.

6. *Total reducing substance in precipitate:* The total amount of reducing substance in the precipitate obtained as described above was determined in the same manner as for total reducing substance in mucus. In some cases the specimen was divided into aliquots after hydrolysis and neutralization. One aliquot was used for the determination of total reducing substance, and the other was fermented with yeast.

*Twenty grams of baker's yeast were washed three times with 50 c.c. portions of distilled water and were then suspended in 50 c.c. of water. Three c.c. of this suspension were centrifuged and the cells were used for the fermentation study.¹⁷

THE DETERMINATION OF REDUCING SUBSTANCES IN HUMAN CERVICAL MUCUS*

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IT IS now known that the cervical mucus of normally menstruating women is most abundant, most translucent and acellular, and possessed of lowest viscosity at midcycle, i.e., when ovulation is believed to occur.¹⁻⁷ The viscosity of cervical mucus is believed to be an important factor in governing the ease with which the spermatozoa can invade this medium, since they can penetrate the mucus for an appreciable distance only at the time of lowest viscosity.^{1-4, 7, 8} Other properties of the mucus may, however, be operative in aiding or hindering the migration of spermatozoa through the cervical canal.

The widespread distribution of glycogen and its hydrolytic products in the female generative tract would appear to have functional significance. According to Hughes⁹ and Novak,¹⁰ glycogen serves as an important nutritive agent for the ovum before and after nidation. Similarly, the presence of glucose in the seminal fluid seems to be important for sperm nutrition. According to McCarthy¹¹ the concentration of glucose in the fresh ejaculate, which averages 300 milligrams per cent,¹¹⁻¹³ is reduced to 10 to 25 per cent of this level by incubation of the semen for twenty-four hours. This diminution suggests utilization of glucose by the spermatozoa. MacLeod^{14, 15} found that the metabolism of human spermatozoa suspended in Ringer-glucose solution is largely glycolytic and that substrates containing such sugars as glucose, maltose, mannose, fructose, and glycogen are required for glycolysis and for the prolonged activity of the spermatozoa. He also suggested¹⁵ that there may be a suitable substrate in the female generative tract to maintain the motility of the spermatozoa, since it would appear that individual spermatozoa carry with them no appreciable quantity of extracellular nutritive matter when they invade the cervical mucus. This suggestion led to the present study of the presence of glucose, related reducing substances, or their precursors in cervical mucus.

Methods

Subjects.—Young healthy women who had normal menstrual histories and normal pelvic structures served as subjects for this study.

Collection of Mucus.—An unlubricated speculum was inserted to expose the cervix. Mucus covering the area of the external os was aspirated with a glass cannula of known weight. Specimens obtained in this manner were considered as "draining" specimens. These were undoubtedly contaminated to varying degrees by the vaginal contents. The cervical canal was then aspirated as completely as possible with a second glass cannula of known weight, and the material thus procured was considered a "canal" specimen. The filled cannulae were weighed and the amount of mucus was determined by difference. Analyses were carried out separately on both types of specimens.

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TABLE II. FREE REDUCING SUBSTANCE IN CERVICAL MUCUS

| | DRAINING SPECIMENS | | | CANAL SPECIMENS | | |
|----------------------------------|---------------------|-----------------|----------------------|---------------------|-----------------|----------------------|
| | PRE-OVULATORY PHASE | OVULATORY PHASE | POST-OVULATORY PHASE | PRE-OVULATORY PHASE | OVULATORY PHASE | POST-OVULATORY PHASE |
| Number of specimens | 16 | 12 | 34 | 22 | 28 | 32 |
| Number of subjects | 5 | 5 | 5 | 5 | 5 | 4 |
| Number of cycles | 8 | 6 | 7 | 8 | 6 | 6 |
| Range, mg. per cent | 50-300 | 30-100 | 60-280 | 40-340 | 0-80 | 50-340 |
| Average, mg. per cent* | 130 | 52 | 133 | 122 | 37 | 150 |
| Standard deviation | 75 | 18 | 63 | 71 | 22 | 65 |
| Averaged on basis of opalescence | | | | | | |
| Marked | 131 (15)† | 70 (2) | 135 (33) | 153 (12) | ---- | 163 (24) |
| Moderate | | 50 (7) | 60 (1) | 91 (8) | 70 (2) | 114 (5) |
| Negligible | 110 (1) | 43 (3) | ---- | 55 (2) | 35 (26) | 107 (3) |

*The probabilities (P) of significant differences in free reducing substance have been calculated by use of the Fisher "t."

Draining: Preovulatory compared to ovulatory, P = 0.0008
 Postovulatory compared to ovulatory, P = <0.0001
 Preovulatory compared to postovulatory, P = 0.9
 Canal: Preovulatory compared to ovulatory, P = <0.0001
 Postovulatory compared to ovulatory, P = <0.0001
 Preovulatory compared to postovulatory, P = 0.15

†Number of specimens indicated in parentheses.

TABLE III. TOTAL REDUCING SUBSTANCE IN CERVICAL MUCUS

| | DRAINING SPECIMENS | | | CANAL SPECIMENS | | |
|----------------------------------|---------------------|-----------------|----------------------|---------------------|-----------------|----------------------|
| | PRE-OVULATORY PHASE | OVULATORY PHASE | POST-OVULATORY PHASE | PRE-OVULATORY PHASE | OVULATORY PHASE | POST-OVULATORY PHASE |
| Number of specimens | 19 | 27 | 56 | 35 | 65 | 56 |
| Number of subjects | 7 | 7 | 9 | 7 | 9 | 9 |
| Number of cycles | 8 | 10 | 15 | 11 | 14 | 16 |
| Range, mg. per cent | 250-1160 | 160-990 | 360-1490 | 300-1480 | 110-640 | 290-2200 |
| Average, mg. per cent* | 688 | 438 | 848 | 728 | 266 | 875 |
| Standard deviation | 226 | 192 | 253 | 270 | 114 | 308 |
| Averaged on basis of opalescence | | | | | | |
| Marked | 720 (13)† | ---- | 881 (51) | 825 (11) | ---- | 963 (42) |
| Moderate | 620 (6) | 598 (10) | 537 (3) | 802 (15) | 560 (2) | 596 (7) |
| Negligible | ---- | 344 (17) | 495 (2) | 488 (9) | 256 (63) | 626 (7) |

*The probabilities (P) of significant differences in total reducing substance have been calculated by use of the Fisher "t."

Draining: Preovulatory compared to ovulatory, P = 0.001
 Postovulatory compared to ovulatory, P = <0.0001
 Preovulatory compared to postovulatory, P = 0.022
 Canal: Preovulatory compared to ovulatory, P = <0.0001
 Postovulatory compared to ovulatory, P = <0.0001
 Preovulatory compared to postovulatory, P = 0.016

†Number of specimens indicated in parentheses.

so small as to be of questionable significance. These precipitates were not washed, since the amount of material obtained was very small, and it may be that a small amount of the supernatant solution remained in the tube and contributed to the values obtained.

Although a positive iodine test suggesting the presence of glycogen is given by the precipitate from the precipitation method, the amount of fermentable material measured after hydrolysis is not sufficient to indicate that this precipitate is glycogen alone. The evidence indicates that this precipitate contains other reducing substances which are not fermentable.

Calculation of results: The cycles, exclusive of the menstrual period, were divided into three phases. The ovulatory phase encompassed those days in midcycle on which the amount of mucus was markedly increased. The pre-ovulatory phase took in the period between the last day of menstruation and the ovulatory phase, and the postovulatory phase, the period from the end of the ovulatory phase to the onset of the next menstrual period. The daily results from all the cycles studied were averaged according to the phase of the cycle and grouped for comparison.

Wherever possible the data were subjected to a statistical analysis and the probabilities (P) as calculated by use of the Fisher "t" are given in the tables. When the value of P was less than 0.05, the differences were considered to be significant.

Results

In a preliminary publication¹⁸ cyclic variations in the water content and in the concentration of reducing substances of cervical mucus were described. The water content (Table I) increases significantly in the ovulatory phase for

TABLE I. WATER CONTENT OF CERVICAL MUCUS

| | DRAINING SPECIMENS | | | CANAL SPECIMENS | | |
|-------------------------------------|----------------------------|-------------------------|-----------------------------|----------------------------|-------------------------|-----------------------------|
| | PRE- OVULATORY PHASE | OVULA- TORY PHASE | POST- OVULATORY PHASE | PRE- OVULATORY PHASE | OVULA- TORY PHASE | POST- OVULATORY PHASE |
| Number of specimens | 38 | 33 | 51 | 33 | 48 | 50 |
| Number of subjects | 3 | 3 | 3 | 3 | 3 | 3 |
| Number of cycles | 9 | 10 | 10 | 9 | 10 | 10 |
| Range, per cent water | 90.2-96.6 | 93.1-97.7 | 90.5-96.3 | 93.9-98.6 | 96.0-98.8 | 91.4-97.0 |
| Average, per cent water* | 93.6 | 95.2 | 93.0 | 95.9 | 97.9 | 94.8 |
| Standard deviation | 2.7 | 2.7 | 1.8 | 2.0 | 2.2 | 2.9 |
| Averaged on basis of opalescence | | | | | | |
| Marked | 93.5 (31)† | 94.4 (7) | 93.0 (51) | 95.5 (14) | ----- | 94.4 (34) |
| Moderate | 94.2 (7) | 95.3 (20) | ----- | 96.2 (16) | 97.2 (5) | 95.7 (15) |
| Negligible | ----- | 96.0 (6) | ----- | 96.6 (3) | 98.0 (43) | 95.8 (1) |

*The probabilities (P) of significant differences in water content have been calculated by the use of the Fisher "t."

| | | |
|-----------|---|-------------|
| Draining: | Preovulatory compared to ovulatory, | P = 0.014 |
| | Postovulatory compared to ovulatory, | P = 0.0001 |
| | Preovulatory compared to postovulatory, | P = 0.23 |
| Canal: | Preovulatory compared to ovulatory, | P = <0.0001 |
| | Postovulatory compared to ovulatory, | P = <0.0001 |
| | Preovulatory compared to postovulatory, | P = 0.5 |

†Number of specimens indicated in parentheses.

both draining and canal samples, although the water content of the draining specimens is consistently lower than for the canal specimens. This difference between the two types of specimens proved to be statistically significant.

The concentration of reducing substances as determined by the various methods are shown in Tables II to VII. With the single exception of the per cent fermentable reducing substance in the draining specimens, which showed no cyclic variation, there is a significant decrease in the concentration of reducing substance in the ovulatory phase of the cycle. This decrease is real and not merely due to dilution, for the concentration is lower in the ovulatory phase even when the calculations are made on a dry weight basis (Table VIII).

There is very little, if any, free reducing substance in the precipitate obtained by the precipitation method (Table V). Many values actually were zero, and for many more the amount of thiosulfate needed in the titration was

TABLE VI. FREE REDUCING SUBSTANCE IN SUPERNATANT

| | DRAINING SPECIMENS | | | CANAL SPECIMENS | | |
|----------------------------------|---------------------|-----------------|----------------------|---------------------|-----------------|----------------------|
| | PRE-OVULATORY PHASE | OVULATORY PHASE | POST-OVULATORY PHASE | PRE-OVULATORY PHASE | OVULATORY PHASE | POST-OVULATORY PHASE |
| Number of specimens | 5 | 9 | 16 | 12 | 35 | 19 |
| Number of subjects | 3 | 5 | 4 | 5 | 5 | 4 |
| Number of cycles | 3 | 6 | 5 | 5 | 7 | 4 |
| Range, mg. per cent | 60-140 | 20-60 | 50-300 | 60-320 | 20-70 | 0-220 |
| Average, mg. per cent* | 96 | 40 | 154 | 124 | 38 | 123 |
| Standard deviation | 33 | 14 | 54 | 68 | 15 | 54 |
| Averaged on basis of opalescence | | | | | | |
| Marked | 100 (4)† | ----- | 161 (15) | 157 (6) | ----- | 145 (14) |
| Moderate | 80 (1) | 50 (1) | 50 (1) | 92 (5) | ----- | 75 (2) |
| Negligible | ----- | 39 (8) | ----- | 90 (1) | 38 (35) | 80 (2) |

*The probabilities (P) of significant differences in free reducing substance in the supernatant have been calculated by the use of the Fisher "t."

Draining: Not enough samples for statistical analysis.

Canal: Preovulatory compared to ovulatory, P = 0.0001
Postovulatory compared to ovulatory, P = <0.0001
Preovulatory compared to postovulatory, P = 1.0

†Number of specimens indicated in parentheses.

TABLE VII. TOTAL REDUCING SUBSTANCE IN PRECIPITATE

| | DRAINING SPECIMENS | | | CANAL SPECIMENS | | |
|----------------------------------|---------------------|-----------------|----------------------|---------------------|-----------------|----------------------|
| | PRE-OVULATORY PHASE | OVULATORY PHASE | POST-OVULATORY PHASE | PRE-OVULATORY PHASE | OVULATORY PHASE | POST-OVULATORY PHASE |
| Number of specimens | 22 | 28 | 35 | 33 | 63 | 41 |
| Number of subjects | 3 | 4 | 5 | 4 | 6 | 6 |
| Number of cycles | 7 | 8 | 8 | 8 | 11 | 9 |
| Range, mg. per cent | 90-270 | 40-560 | 120-670 | 40-300 | 0-190 | 60-630 |
| Average, mg. per cent* | 310 | 173 | 285 | 145 | 60 | 192 |
| Standard deviation | 150 | 129 | 112 | 68 | 43 | 115 |
| Averaged on basis of opalescence | | | | | | |
| Marked | 303 (18)† | 305 (2) | 298 (32) | 181 (16) | ----- | 229 (28) |
| Moderate | 340 (4) | 168 (24) | 143 (3) | 110 (15) | 73 (6) | 108 (11) |
| Negligible | ----- | 100 (2) | ----- | 130 (2) | 58 (57) | 135 (2) |

*The probabilities (P) of significant differences in total reducing substance in the precipitate have been calculated by use of the Fisher "t."

Draining: Preovulatory compared to ovulatory, P = 0.0013
Postovulatory compared to ovulatory, P = 0.0007
Preovulatory compared to postovulatory, P = 0.5
Canal: Preovulatory compared to ovulatory, P = <0.0001
Postovulatory compared to ovulatory, P = <0.0001
Preovulatory compared to postovulatory, P = 0.029

†Number of specimens indicated in parentheses.

mucus since the amount of fermentable material after hydrolysis accounts for less than 50 per cent of the total amount of reducing substance measured (Table IV).

Theoretically, the sum of the total amount of reducing substance obtained by hydrolysis of both the precipitate and the supernatant from the precipitation method should equal the total amount of reducing substance obtained by direct hydrolysis of the mucus. However, on direct hydrolysis a much higher concentration was always obtained. The supernatant is strongly alkaline and it may be that this has a deleterious effect on whatever reducing substances are contained in it. Further investigation into this fraction is necessary before definite conclusions can be drawn.

TABLE IV. PER CENT FERMENTABLE REDUCING SUBSTANCE

| | DRAINING SPECIMENS | | | CANAL SPECIMENS | | |
|----------------------------------|----------------------------|-------------------------|-----------------------------|----------------------------|-------------------------|-----------------------------|
| | PRE- OVULATORY PHASE | OVULA- TORY PHASE | POST- OVULATORY PHASE | PRE- OVULATORY PHASE | OVULA- TORY PHASE | POST- OVULATORY PHASE |
| Number of specimens | 10 | 9 | 27 | 17 | 39 | 21 |
| Number of subjects | 4 | 4 | 8 | 5 | 7 | 8 |
| Number of cycles | 4 | 5 | 10 | 6 | 9 | 11 |
| Range, per cent fermentable | 36.4-76.7 | 39.5-77.8 | 28.0-80.7 | 23.9-71.6 | 8.7-62.5 | 28.6-77.9 |
| Average, per cent fermentable* | 54.8 | 60.8 | 59.9 | 44.6 | 36.4 | 50.7 |
| Standard deviation | 12.5 | 11.5 | 12.7 | 13.8 | 13.4 | 12.3 |
| Averaged on basis of opalescence | | | | | | |
| Marked | 57.1 (8)† | ---- | 59.9 (26) | 49.5 (8) | ---- | 51.7 (20) |
| Moderate | 45.8 (2) | 65.6 (5) | ---- | 39.2 (8) | ---- | 28.6 (1) |
| Negligible | | 54.7 (4) | 59.5 (1) | 48.1 (1) | 36.4 (39) | ---- |

*The probabilities (P) of significant differences in per cent fermentable glucose have been calculated by use of the Fisher "t."

Draining: Preovulatory compared to ovulatory, P = 0.35
Postovulatory compared to ovulatory, P = 0.85
Preovulatory compared to postovulatory, P = 0.27
Canal: Preovulatory compared to ovulatory, P = 0.038
Postovulatory compared to ovulatory, P = <0.0001
Preovulatory compared to postovulatory, P = 0.15

†Number of specimens indicated in parentheses.

TABLE V. FREE REDUCING SUBSTANCE IN PRECIPITATE

| | DRAINING SPECIMENS | | | CANAL SPECIMENS | | |
|----------------------------------|----------------------------|-------------------------|-----------------------------|----------------------------|-------------------------|-----------------------------|
| | PRE- OVULATORY PHASE | OVULA- TORY PHASE | POST- OVULATORY PHASE | PRE- OVULATORY PHASE | OVULA- TORY PHASE | POST- OVULATORY PHASE |
| Number of specimens | 5 | 9 | 17 | 12 | 35 | 20 |
| Number of subjects | 3 | 5 | 4 | 5 | 5 | 4 |
| Number of cycles | 3 | 6 | 5 | 5 | 7 | 5 |
| Range, mg. per cent | 10-30 | 0-20 | 0-100 | 0-60 | 0-20 | 0-100 |
| Average, mg. per cent | 24 | 7 | 28 | 17 | 6 | 25 |
| Standard deviation | 8 | 6 | 30 | 22 | 7 | 32 |
| Averaged on basis of opalescence | | | | | | |
| Marked | 24 (5)* | ---- | 29 (16) | 23 (6) | ---- | 31 (15) |
| Moderate | ---- | 10 (1) | 10 (1) | 6 (5) | ---- | 0 (3) |
| Negligible | ---- | 6 (8) | ---- | 30 (1) | 6 (35) | 15 (2) |

*Number of specimens indicated in parentheses.

It is interesting to note that the concentration of free reducing substance as measured in cervical mucus directly (Table II) and the concentration of free reducing substance in the supernatant (Table VI) are strikingly similar. This supernatant gives a positive biuret reaction while the corresponding precipitate does not. The mucus itself also gives a positive biuret test. Hewitt¹⁹ has shown that tyrosine and tryptophane will reduce the Hagedorn-Jensen reagent used for determining glucose almost as well as glucose itself. The presence of tyrosine and tryptophane in cervical mucus has been previously shown,¹⁸ and it may well be that these, and possibly other amino acids, are contributing to the reduction of the copper reagent. These may also contribute appreciably to the amount of total reducing substance in cervical

can be found in mucus aspirated from within the cervical canal as long as thirty-six to eighty hours after coitus.²⁰⁻²² Even though many spermatozoa probably penetrate beyond the cervical canal so quickly in the ovulatory phase of the cycle as to have no need of a substrate as far as the cervical canal is concerned, the fact that those remaining in the canal are still motile many hours later suggests that some utilizable substrate is available to them there.

The data from the present studies show that the concentration of fermentable reducing substance present in the cervical mucus in the canal in the ovulatory phase, even though it is significantly lower than in the pre- and post-ovulatory phases, is still 97 milligrams per cent. This is well within the range of concentration of 20 to 200 milligrams per cent as determined by MacLeod.¹⁴

Summary

In the ovulatory phase of the normal menstrual cycle when the quantity of cervical mucus is greatest, the water content is increased and the cell count, as estimated on the basis of opalescence, is decreased. Throughout the menstrual cycle the mucus is found to contain free reducing substance. On hydrolysis additional quantities of reducing substance are found, approximately 50 per cent of which are fermentable with yeast. When cervical mucus is alkalinized and alcohol is added, a precipitate is formed which yields appreciable quantities of reducing substance only after hydrolysis. The supernatant contains free reducing substances in amounts comparable to the free reducing substance in mucus itself. Since the presence of amino acids has been demonstrated in cervical mucus it is suggested that these contribute to the measurement of reducing substance in some of the fractions. These various reducing substances are present in lowest concentration in the ovulatory phase, even when calculated on a dry weight basis. The possible significance of these findings with reference to sperm metabolism is discussed.

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TABLE VIII. PER CENT CONCENTRATION OF REDUCING SUBSTANCES IN CERVICAL MUCUS
CALCULATED ON A DRY WEIGHT BASIS

| | DRAINING SPECIMENS | | | CANAL SPECIMENS | | |
|---|----------------------------|-------------------------|-----------------------------|----------------------------|-------------------------|-----------------------------|
| | PRE- OVULATORY PHASE | OVULA- TORY PHASE | POST- OVULATORY PHASE | PRE- OVULATORY PHASE | OVULA- TORY PHASE | POST- OVULATORY PHASE |
| Free reducing substance in cervical mucus | 2.03 | 1.08 | 1.90 | 2.98 | 1.76 | 2.88 |
| Total reducing substance in cervical mucus | 10.75 | 9.13 | 12.11 | 17.76 | 12.67 | 16.83 |
| Free reducing substance in precipitate | 0.38 | 0.15 | 0.40 | 0.41 | 0.29 | 0.48 |
| Free reducing substance in supernatant | 1.50 | 0.83 | 2.20 | 3.02 | 1.81 | 2.37 |
| Total reducing substance in precipitate | 4.84 | 3.60 | 4.07 | 3.54 | 2.86 | 3.69 |

One of the most striking changes occurring at midcycle is the altered appearance of the cervical mucus.¹⁻⁷ Prior to the ovulatory phase the mucus is very cellular, giving it an opalescent appearance. Coincident with the increase in amount and increase in water content is a marked decrease in cellularity. The mucus becomes translucent and only very small patches of cellular material are occasionally visible to the naked eye. It has not been possible to determine the opalescence of cervical mucus in an objective fashion because of the difficulty in obtaining a satisfactory dispersal of the mucus with its cells over a grille. Therefore the opalescence has been estimated subjectively as marked, moderate, or negligible. Even this approximation has been sufficient to indicate a possible relationship between the degree of opalescence and both the water content and the concentration of reducing substances. It can be seen in the various tables that in general the more marked the opalescence the less the water content and the greater the concentration of reducing substances. To determine whether the chemical constituents found in cervical mucus are contained within the cells themselves or are in the extracellular portion is a problem for future study. The draining specimens are undoubtedly contaminated by the vaginal contents and only rarely is a completely translucent draining specimen obtained in midcycle as compared to the invariably clear canal samples procured at this time. The draining specimens contain significantly less water in all three phases of the cycle and significantly more reducing substance in the ovulatory phase than do the canal specimens.

Discussion

At present we may only speculate as to the significance of these findings. As stated earlier, MacLeod has shown that spermatozoa require a utilizable carbohydrate such as glucose, fructose, maltose, mannose or glycogen as a substrate in order to maintain their motility.^{14, 15} He has also shown that in a glucose-free medium at body temperature many spermatozoa lose their motility completely within as short a time as two hours, whereas if adequate glucose is present and the oxygen tension is low, maximal motility is retained at least twelve hours in vitro.¹⁵ He has determined that the effective concentration of utilizable sugar lies between 20 and 200 milligrams per cent.¹⁴

It is unlikely that spermatozoa carry with them any appreciable quantity of glucose from the semen as they enter the cervical mucus, yet motile sperm

The first month is utilized as a control. No attempt at conception is advised during this month. This control month supplies information upon whether there is any ovulation activity that can be detected, whether detectable activity is normal or abnormal, and if normal, the day in the cycle when ovulation takes place. Our evidence indicates that the egg is ready for fertilization on the last day of the color reaction.

During the months following the control month, intercourse is advised, or artificial insemination is performed on the last day of each normal ovulation reaction. No attempt at conception is advised, however, if the reaction is not normal.

Intercourse is interdicted during every testing period, since the act affects adversely the color reaction. It is especially important that intercourse is not practiced on the days immediately prior to the day when the egg is ready for fertilization, otherwise there will not be the maximum number of sperm available for that day.

Results

Ten women became pregnant when coitus or artificial insemination was timed with the day of ovulation. All but one of these patients had had difficulty in conceiving, prior to the time of her successful impregnation.

CASE 1.—This patient had been married for seven years. For three and one-half years she had been unable to become pregnant. Her husband was found to have no sperm cells. The patient's Fallopian tubes were revealed to be patent by uterosalpingography.

The details of the ovulation timing appear in Table I. The menstrual cycles were quite regular, and the patient's ovulation reactions with one exception were normal. Intrauterine insemination with the cells of a donor was practiced twice. In the first instance the insemination failed. It is believed that this failure was due to the fact that the semen of the first donor contained only 12,000,000 moving sperm cells in the total ejaculate.

The second insemination was successful. The semen of this donor contained 228,000,000 moving sperm cells in the total ejaculate.

TABLE I. CASE 1

| OVULATION TESTS | MENSTRUAL CYCLE | | COMMENTS |
|-----------------|------------------------|----------------|--|
| | OVULATION ON CYCLE DAY | LENGTH IN DAYS | |
| 1 | 12 | 26 | Control month. Reaction normal |
| 2 | 12 | 26 | Donor infertile. Intrauterine insemination failed |
| 3 | Abnormal | 27 | No attempt to conceive |
| 4 | 13 | 27 | Control month. Reaction normal |
| 5 | 13 | -- | Donor fertile. Intrauterine insemination 2 p.m. Ovulation cycle day 13—conception followed |

CASE 2.—This patient had been married for ten years without becoming pregnant. Her husband was normally fertile with 238,000,000 moving cells in the total ejaculate. The fimbriated ends of both Fallopian tubes of the patient were discovered to be closed by uterosalpingography. Bilateral salpingostomy was performed.

The details of the ovulation timing appear in Table II. Three attempts at conception were made following salpingostomy. Two of these were unsuccessful. The first failure is explained on the ground that the ovulation reaction was abnormal. The second failure is explained on the fact that coitus occurred on days 8 and 9 of the menstrual cycle when ovulation took place on day 10. The

CONCEPTION FOLLOWING THE PREDICTION OF THE DAY OF OVULATION WITH THE RAT TEST*

A Study of Ten Patients

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IN A previous communication, one of us (E. J. F.), described a new method for predicting the probable day of ovulation in women,¹ and in a following paper, reported some observations on the accuracy of the procedure as indicated by immediate laparotomy upon the monkey.²

Utilizing this test in the study of relatively infertile couples, intercourse or artificial insemination practiced on the predicted day of ovulation has resulted in some 50 conceptions. The present report deals with 11 conceptions experienced by 10 patients who came under the observation of both authors. The observations made in the handling of these women illustrate the use of the method, and indicate some of the problems which have been encountered in its application.

Materials and Methods

The first step in the study of each couple was an analysis of the husband's semen. The second procedure was an investigation of the patency of the wife's Fallopian tubes. This was followed by a timing of the day of ovulation.

Investigation of Husband.—The semen was analyzed following five days of sexual abstinence. The husband was then classified as being (1) infertile, (2) low fertile, or (3) highly fertile. The criteria for this classification will be described in a later publication by one of us (E. J. F.). The sperm counts recorded in this report refer to the total number of moving cells in the whole ejaculate.³

Investigation of the Wife.—In the absence of previous pregnancies or laparotomies, the patency of the Fallopian tubes usually was determined by uterosalpingography.

The probable date of ovulation was detected by the use of the rat test.

Specimens of urine collected on 10 consecutive days during the middle third of the patient's menstrual month were tested.

The technique of the test is as follows: 2 c.c. of the urine which the patient passes on arising in the morning are injected subcutaneously into each of two immature, female white rats of the Wistar strain. Each animal is killed by illuminating gas at the end of two hours. The abdomen is opened; the 2 ovaries are drawn, one at a time, into the wound, and the color of each is compared with the graded shades of red of the Munsell color system.

In the presence of normal ovulation, the patient's urine induces hyperemia in the ovaries of the rat on four or five consecutive days. In the total absence of ovulation, there is no hyperemia of the rats' ovaries. If the ovulation process is abnormal, hyperemia occurs, but usually not on four consecutive days. Intercourse is interdicted during the urine testing period of each month.

*This investigation was aided by a grant from The Samuel S. Fels Fund.

TABLE IV. CASE 4

| OVULATION TESTS | MENSTRUAL CYCLE | | COMMENTS |
|-----------------|------------------------|----------------|---|
| | OVULATION ON CYCLE DAY | LENGTH IN DAYS | |
| 1 | 14 | 26 | Coitus on cycle day 11 and for 4 consecutive days. Failure due to wrong timing of coitus and low sperm count on day of ovulation |
| 2 | 13 | 25 | Coitus on cycle day 11, second day of color, and repeated next day. Failure due to wrong timing of coitus and low sperm count on day of ovulation |
| 3 | Abnormal | 27 | Coitus on days 12, 13, and 14. No conception predicted on account of abnormal reaction |
| 4 | 11 | 26 | Coitus on cycle day 8 and for 4 consecutive days. Failure predicted on account of failure in timing and low sperm count on day of ovulation |
| 5 | 11 | 26 | Coitus on cycle day 12, and on 2 following days during a negative reaction. Failure predicted on account of wrong timing. Ovulation had occurred |
| 6 | 11 | -- | Coitus on cycle day 11, the fourth day of color reaction. Conception occurred |

One failure to conceive was due to the presence of an abnormal ovulation reaction. The last failure was due to the fact that coitus was practiced for the first time on the day after the ovulation reaction had ended.

The successful coitus took place on the predicted day of ovulation, which was the fourth and last day of a normal color reaction. It was also day 11 of the menstrual cycle.

CASE 5.—This patient had been married for thirteen years and had had two planned pregnancies. Her husband was highly fertile, possessing a sperm count of 300,000,000 moving cells in the entire ejaculate. No test of tubal patency was made.

The ovulation timing is shown in Table V.

TABLE V. CASE 5

| OVULATION TESTS | MENSTRUAL CYCLE | | COMMENTS |
|-----------------|------------------------|-------------------|--|
| | OVULATION ON CYCLE DAY | LENGTH IN DAYS | |
| 1 | 8 | Average (25 days) | Conception followed 1 coitus on eighth day |

Ovulation was tested only once. It took place on the eighth day of an average 25-day cycle. Coitus on this day was followed by conception.

CASE 6.—This patient had been married for two and one-half years, and had failed to conceive for two years. Her husband was declared to be practically sterile by a urologist, and was treated with gonadogen. The patency of the wife's Fallopian tubes was proved by uterosalpingography.

The record of ovulation timing appears in Table VI.

Coitus was practiced during two months of testing. The first attempt failed. This is explained on the ground that the ovulation reaction was abnormal, and also because coitus was practiced two days before the probable day of ovulation.

The successful coitus was performed twice on the last day of a normal 4-day rat color reaction, which was day 9 of an average 26-day cycle.

natural decrease in the sperm count, which normally occurs following closely repeated ejaculations, probably accounted for the failure in this instance.

TABLE II. CASE 2

| OVULATION TESTS | MENSTRUAL CYCLE | | COMMENTS |
|-----------------|------------------------|----------------|---|
| | OVULATION ON CYCLE DAY | LENGTH IN DAYS | |
| 1 | 11 | 27 | Control month. Reaction normal |
| 2 | Abnormal | 30 | Coitus P.M. cycle day 9 and A.M. cycle day 10. Failure due to abnormal reaction |
| 3 | 10 | 25 | Coitus P.M. cycle days 8 and 9. Failure due to reduced sperm count from coitus prior to ovulation |
| 4 | Abnormal | 28 | No coitus |
| 5 | 12 | -- | Coitus on cycle day 12. Conception followed |

The successful coitus took place on the day of ovulation which was day 12 of the cycle. It was the last day of a 4-day color in the rat ovaries. A tubal gestation resulted which was terminated by salpingectomy.

CASE 3.—This patient had been married for five years with inability to become pregnant for two years. Her husband's semen contained 266,000,000 moving cells in the entire ejaculate. The wife's Fallopian tubes were proved to be patent by uterosalpingography.

The details of the ovulation timing appear in Table III.

TABLE III. CASE 3

| OVULATION TESTS | MENSTRUAL CYCLE | | COMMENTS |
|-----------------|------------------------|----------------|---|
| | OVULATION ON CYCLE DAY | LENGTH IN DAYS | |
| 1 | Abnormal (13) | 25 | Seven-day color reaction. Ovulation probably on cycle day 13 |
| 2 | Abnormal (11) | 25 | Six-day color reaction. Ovulation probably on cycle day 11 |
| 3 | 11 | -- | Coitus on cycle day 11, the fourth day of color reaction. Conception followed |

Ovulation was timed through three consecutive months. The ovulation reactions of the first two months were abnormal. Conception occurred during the first normal month, when coitus was practiced on the fourth day of the rat color reaction, which was the eleventh day of the menstrual cycle.

CASE 4.—This patient had been married for eighteen months with inability to conceive for the last twelve months. Her husband was reported by a urologist to be, in all probability, sterile. The patency of the wife's tubes was not tested.

The details of the ovulation timing appear in Table IV.

Ovulation day was timed for a period of six months. The reaction was normal five times. Coitus was practiced during each of the six months of testing. It failed to result in conception five times. Three of the failures can be explained on the ground that coitus was performed before the day of ovulation. In the first of these three months, it was practiced on day 11 when ovulation took place on day 14. In the second month, it was performed on day 11 when ovulation occurred on day 13. The third of these three failures was due to the fact that coitus was practiced on day 8 when ovulation took place on day 11. Repeated coitus, previous to the day of ovulation, results in a lowered sperm count on the day of ovulation.

Ovulation was timed during five consecutive months. For three months, the ovulation reaction was abnormal, and one month was used as a control. Coitus was practiced, but conception failed during two of the months when the reaction was abnormal. The fifth month produced a normal 4-day rat color reaction, which resulted in ovulation on the tenth day of the cycle. Conception followed coitus practiced on that day. The selection of that day was based upon timing and observations which were carried out during the preceding months.

CASE 9.—This patient was married for 11 years. She had had one miscarriage previously, but had failed to conceive for the last seven years. Her husband's semen contained 308,000,000 moving cells in the total ejaculate. The patency of the wife's Fallopian tubes was proved by uterosalpingography.

The details of the ovulation timing appear in Table IX.

TABLE IX. CASE 9

| OVULATION TESTS | MENSTRUAL CYCLE | | COMMENTS |
|-----------------|------------------------|----------------|--|
| | OVULATION ON CYCLE DAY | LENGTH IN DAYS | |
| 1 | 8 | 24 | Control month |
| 2 | 9 | -- | Coitus on ovulation cycle day. Conception followed |

The menstrual cycles of this patient were quite regular, and her ovulation reaction during the control month was normal, occurring on day 8 of her cycle.

Conception occurred during the first test month on the fifth day of the rat color reaction which was cycle day 9.

CASE 10.—Patient married for six years with failure of conception to occur for one and one-half years. Wife Rh negative, husband Rh positive. Husband relatively infertile for several months in the early months of ovulation timing, but judged to be fertile in the remainder of the ovulation timing period. Patency of wife's left Fallopian tube confirmed by uterosalpingography. Patency of right tube equivocal.

The details of the ovulation timing appear in Table X.

TABLE X. CASE 10

| OVULATION TESTS | MENSTRUAL CYCLE | | COMMENTS |
|-----------------|------------------------|----------------|---|
| | OVULATION ON CYCLE DAY | LENGTH IN DAYS | |
| 1 | 16 | 28 | Coitus days 15 and 16. Sperm count 77 million |
| 2 | 13 | 27 | Coitus days 13 and 14. Still low sperm count |
| 3 | Abnormal | 28 | Coitus days 13, 14 |
| 4 | Abnormal | 31 | Coitus day 12 |
| 5 | 13 | 26 | Coitus days 13 and 14 |
| 6 | 12 | 26 | Coitus days 11, 12, 13 |
| 7 | 13 | 28 | Insemination day 13. Coitus day 14 |
| 8 | 12 | 26 | Insemination day 13. Prediction--no conception |
| 9 | 13 | 26 | Coitus days 13, 14, 15 |
| 10 | 14 | 26 | Coitus day 14 |
| 11 | 11 | -- | Intrauterine insemination day 11. Conception followed |

Ovulation was timed for ten months before conception took place during the eleventh month. The 10 failures are explained on the following grounds: Tests 1 and 2, husband infertile. Tests 3 and 4, ovulation reactions abnormal.

TABLE VI. CASE 6

| OVULATION TESTS | MENSTRUAL CYCLE | | COMMENTS |
|-----------------|------------------------|----------------|---|
| | OVULATION ON CYCLE DAY | LENGTH IN DAYS | |
| 1 | Abnormal (11) | 25 | Control month. Abnormal reaction following uterosalpingography. Ovulation probably cycle day 11 |
| 2 | 11 | 26 | Control month. Dilatation and curettage |
| 3 | Abnormal (11) | 28 | Coitus on cycle days 9 and 10. Failure anticipated due to wrong timing and to abnormal reaction |
| 4 | 9 | -- | Coitus twice on cycle day 9. Conception followed |

TABLE VII. CASE 7

| OVULATION TESTS | MENSTRUAL CYCLE | | COMMENTS |
|-----------------|------------------------|----------------|--|
| | OVULATION ON CYCLE DAY | LENGTH IN DAYS | |
| 1 | 13 | -- | <i>First Pregnancy</i> Coitus day 12, P.M. and day 13, A.M. Conception followed |
| | | | <i>Second Pregnancy</i> |
| 1 | Abnormal | 29 | Control month |
| 2 | 16 | 28 | Coitus on day 14 |
| 3 | 13 | -- | Coitus days 13 and 14. Conception followed |

CASE 7.—This patient had been married for four years and had had one previous pregnancy. Her husband was highly fertile with 373,000,000 moving sperm cells in the total ejaculate. The patency of the wife's Fallopian tubes was not tested.

The details of the ovulation timing appear in Table VII.

This patient was timed for two pregnancies. In the case of the first conception, success was achieved when coitus was practiced at midnight the day before ovulation and early in the morning of the day of ovulation.

Preceding the second conception, three ovulation tests were made. The first ovulation reaction was abnormal. Attempts at conception were made during each of the following test months. The first attempt was a failure. This is explained on the ground that the coitus took place two days before ovulation. The second attempt was successful. Here, coitus was practiced on the day of ovulation and on the succeeding day.

CASE 8.—This patient had been married for five years with failure to conceive for eighteen months. The husband possessed 158,000,000 moving cells in the entire ejaculate. The patency of the wife's Fallopian tubes was proved by uterosalpingography.

The details of the ovulation timing appear in Table VIII.

TABLE VIII. CASE 8

| OVULATION TESTS | MENSTRUAL CYCLE | | COMMENTS |
|-----------------|------------------------|----------------|--|
| | OVULATION ON CYCLE DAY | LENGTH IN DAYS | |
| 1 | Abnormal | 31 | ----- |
| 2 | 12 | 27 | Normal control |
| 3 | Abnormal | 25 | Coitus days 13, 14, 15. Prediction—no conception |
| 4 | Abnormal | 28 | Coitus days 12, 13, 14. Prediction—no conception |
| 5 | 10 | -- | Coitus days 10, 11, 12. Conception followed |

succeeding ovulations, without the necessity of testing each succeeding month for the exact day.

The rat ovulation test has still another important value. It provides knowledge of the day of ovulation prior to the event, and the nature of the reaction is such that it gives two or three days of warning previous to the impending ovulation. This warning is of special value in those cases in which artificial insemination appears to be a necessity, since it allows time for preparation for this procedure. An additional value of the test lies in the fact that it makes unnecessary the carrying out of an endometrial biopsy.

Still another advantage in the use of the rat ovulation test lies in the fact that advance knowledge of the day of ovulation makes it possible to have the husband conserve his sperm cells for that day. In cases where the sperm cells of an anonymous donor are to be employed, knowledge of the exact day of ovulation makes it possible to be economical in the use of such donor specimens.

Summary

1. Conceptions are reported in nine relatively infertile and in one highly fertile woman, aided by the use of the rat ovulation test for the purpose of timing either coitus or artificial insemination with the day of ovulation.

2. The use of the method is described, and some of its advantages are outlined.

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Tests 5, 6 and 7, no explanation available. It is possible that an error in the technique of the insemination can have accounted for the failure in test month 7. Test 8 failure due to fact that insemination was performed after ovulation had taken place. No conception was predicted. At this point, uterosalpingography was performed, which revealed the possible blockage of the right Fallopian tube, which blocking may have been released by the oil employed in the test. The failures in test months 9 and 10 are not explained, unless sperm fail to reach the inside of the uterus.

The successful impregnation followed intrauterine insemination on day 11 of the cycle which was the fourth day of a normal rat color reaction.

Discussion

The present group of observations includes ones upon couples who were studied at various times while the rat test was being developed. It is believed that conception would have taken place earlier in some instances, if as much had been known in the beginning of the study as was known by the time that the last of the present series of patients was investigated.

A total of 47 tests for ovulation was made. Seven control month tests were carried out. Attempts at conception were advised against during these months.

Fourteen tests revealed the presence of abnormal ovulation reactions. Previous experience had indicated that conception will not occur in the presence of such reactions. That observation was confirmed in the present series of patients, where coitus was practiced.

The remaining 26 tests registered normal ovulation reactions. Conception should have occurred in association with the first normal reaction of each patient had all conditions been favorable. Eleven conceptions did take place.

There were 15 failures of which four cannot be explained. Three were due to male infertility, and 11 failures are explained as follows: six resulted from the fact that coitus was practiced on the day immediately preceding the day of ovulation. Coitus on the day prior to ovulation has the probable effect of reducing the sperm count to a point where the male is infertile on the day of ovulation, especially in the case of males of relatively low fertility.

Two other failures can be explained on the ground that coitus did not occur until the day after ovulation. It was advised that intercourse take place at this time in these two instances, in order to check the hypothesis that conception would be unlikely or impossible at this time.

The rat ovulation test appears to have a very definite place in the treatment of the sterile couple. If the urine of the patient does not produce any response in the rat ovary during any month that she is tested, her chance of becoming pregnant is very slight.

Some women, tested during many consecutive months, exhibited few normal ovulation reactions. Knowledge of this state of affairs aids greatly in evaluating their chances of becoming pregnant. It emphasizes the need for testing such women every month in order to discover the few times that they may conceive in any long period of time.

The majority of women ovulate normally each month. When this fact has been established by several tests, it then becomes possible to predict the date of

was delivered by cesarean section and resterilized. The pregnancy in the second patient was terminated within the first trimester of gestation.

The 62 patients in this survey gave birth to 149 viable infants. This included 89 infants delivered after the diagnosis of tuberculosis. There were four premature infants, including one set of twins. The fetal mortality was 1.34 per cent (two deaths). One baby died of intracranial hemorrhage, and the second infant died of prematurity following a cesarean section done in the seventh month of pregnancy because of a fulminating pre-eclampsia.

Inactive Tuberculosis

There were seven patients in this group. All of these patients are living. Four were primiparas and three were multiparas.

All of the primiparas were delivered spontaneously and, on last report, ranging from five to eleven years since their first pregnancy, physical examination, laboratory studies, and serial x-rays of their chests showed the tuberculosis to be inactive. The length of time between the diagnosis of tuberculosis and their first pregnancy ranged from four to eleven years. These patients have since given birth to a total of eight infants. One of these infants was delivered by cesarean section because of a fulminating pre-eclampsia at seven months resulting in a stillborn child.

Two of the three multiparas were delivered spontaneously. The pregnancy was terminated within the first trimester in the third patient, and she was also sterilized because of epilepsy. She had had two term, spontaneous deliveries before the diagnosis of tuberculosis. The other two multiparas gave birth to a total of five term infants after the diagnosis of tuberculosis was made. In one of these patients there was a term delivery one year after the diagnosis of tuberculosis, and on the twenty-fifth postpartum day she had a pulmonary hemorrhage, but on x-ray examination there was no evidence of gross active tuberculosis. Five years later there was questionable activity of the tuberculosis following delivery. With her last pregnancy, four years later, the tuberculosis was considered inactive.

In all of these patients, primiparas and multiparas, pregnancy did not reactivate a tuberculous process which had been considered as inactive.

Quiescent or Latent Tuberculosis

Five patients had quiescent or latent tuberculosis at the time of their first admission to the hospital. There were three primiparas and two multiparas in this group. All of the patients are living and well.

Two primiparas were delivered by cesarean section. In one patient a diagnosis of moderately advanced tuberculosis with a positive sputum was made eight years before her first pregnancy. The second patient became pregnant four years after a diagnosis of tuberculosis. At that time the tuberculosis was considered as moderately advanced. She received active therapy for four years. A cesarean section was done because of a premature separation of the placenta.

PREGNANCY COMPLICATING TUBERCULOSIS

A Survey for an Eleven-Year Period*

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IN AN eleven-year period from January, 1930, to January, 1941, there have been 28,846 patients delivered at the Elizabeth Steel Magee Hospital. This included 103 cases of known pulmonary tuberculosis—an incidence of 0.35 per cent. Clinical surveys for a 5- to 15-year period were available for 62 tuberculous patients. The records of the remaining 41 patients were considered too incomplete to include in this report.

The various extremes from termination of the pregnancy in the first trimester to allowing the pregnancy to go to term were employed in the management of pregnancy in these 62 patients. Abortions were recommended by medical consultants in 24 patients. Twelve patients were delivered by cesarean section, and 26 patients delivered spontaneously. In the majority of the 24 patients aborted, medical consultants recommended sterilization. During this survey period the management of pregnancy complicated by tuberculosis has shown a conservative swing from early termination to spontaneous delivery at term. The grade of tuberculosis varied from arrested cases to far-advanced involvement (Fig. 1).

This survey was composed of 24 primiparas and 38 multiparas. They varied between the ages of 19 and 44 years. Our survey period in these patients varied from 5 to 15 years.

Of the 24 primiparas, pregnancies were terminated within the first trimester in 10, five were delivered by cesarean section; 13 of these patients being sterilized at the time of operation. The remaining nine patients were delivered spontaneously. The second pregnancy in one patient that delivered spontaneously was terminated by cesarean section, and she was sterilized at the time of operation. Sterilization following 1 cesarean section failed, and the second pregnancy was terminated within the first trimester and the patient was resterilized.

Of the 38 multiparas, 16 were delivered spontaneously. In one patient that had had two spontaneous births, the two pregnancies which followed were terminated by cesarean section, sterilization having failed following the first cesarean delivery. Seven patients were delivered by cesarean section and sterilized, and the pregnancies in 15 patients were terminated within the first trimester. In two of the 15 patients aborted therapeutic abortions were performed without sterilization. Two sterilizations failed among the group of 13 patients aborted and sterilized. One patient was allowed to go to term and she

*Read at Meeting of Pittsburgh Obstetrical and Gynecological Society, December 9, 1946.

section and sterilized. On x-ray examination April 20, 1940, there was scattered right upper tuberculosis of minimal extent; her sputum was negative. In 1941 the patient again became pregnant and was delivered at term by cesarean section and resterilized. On x-ray examination Oct. 29, 1942, there was scattered nodular and linear involvement of the right upper lung field with complete collapse of the left lung. On April 20, 1945, the tuberculosis was considered as apparently arrested, and at present the patient is doing well and does all of her own housework.

It is interesting to note that this last patient had far-advanced tuberculosis which was treated by thoracoplasty after pneumothorax and phrenectomy had failed. She had four pregnancies following this. Two pregnancies were terminated by cesarean section. The postpartum and postoperative courses in all of these deliveries were uneventful. There was no reactivity of the tuberculosis.

Unilateral Active Apical or Minimal and Aberrative Tuberculosis

There were 10 patients in this group. Four were primiparas and six were multiparas. One patient is dead—an incidence of 10.0 per cent.

The four primiparas were all considered as arrested cases of tuberculosis six to ten years after their first pregnancy. In one primipara the pregnancy was terminated within the first trimester, but she was not sterilized. Her tuberculosis was also diagnosed five years before her pregnancy. During a six-year interval this same patient gave birth spontaneously to two term infants. The third primipara was delivered by cesarean section and sterilized. The cesarean section was done because of a cephalopelvic disproportion. The tuberculosis was diagnosed during the pregnancy. There was no acute exacerbation of the disease following delivery. In the fourth patient it was evident that the tuberculosis was probably activated by her first pregnancy which terminated spontaneously. However, the tuberculosis was considered as minimal and there was no evidence of activity following her second pregnancy which occurred one year later. Her complete history follows:

CASE 2.—M. E., a gravida i, 27 years of age, white, was admitted to the hospital Jan. 4, 1937. She was at term and was delivered spontaneously. She was discharged Jan. 14, 1937, after an uneventful postpartum course. One month later she was readmitted to the hospital complaining of pain in her chest and cough. She had been having frequent chills and night sweats. She was diagnosed as having a pleural effusion, and this was proved as tuberculous in origin by guinea pig injection. She remained febrile and was finally discharged May 5, 1937, and sent to a tuberculosis sanatorium. The effusion completely disappeared, and she was discharged from the sanatorium on Oct. 19, 1937. When seen six months later she was feeling well and gaining weight; her sputum was negative. On x-ray examination Feb. 4, 1938, there was slight tuberculous involvement of the left second interspace. The patient was next seen July 8, 1938; she was 3½ months pregnant and refused to be aborted and sterilized. She was delivered by low cervical cesarean section and sterilized Jan. 20, 1939. Eight months later there was no evidence of active tuberculosis on routine examination. On re-examination March 6, 1942, there was no evidence of tuberculous activity. At present the patient is well and working.

Six years later both patients were considered as having no evidence of active tuberculosis. Within this interval of time they both gave birth to another term infant by cesarean section. In the third primipara a diagnosis of quiescent tuberculosis was made three years before her pregnancy. The pregnancy was terminated within the first trimester, and the patient was sterilized.

The first multipara was delivered spontaneously of two term infants. The diagnosis of tuberculosis was made during her first pregnancy. The second multipara had four term infants. Her case history is presented.

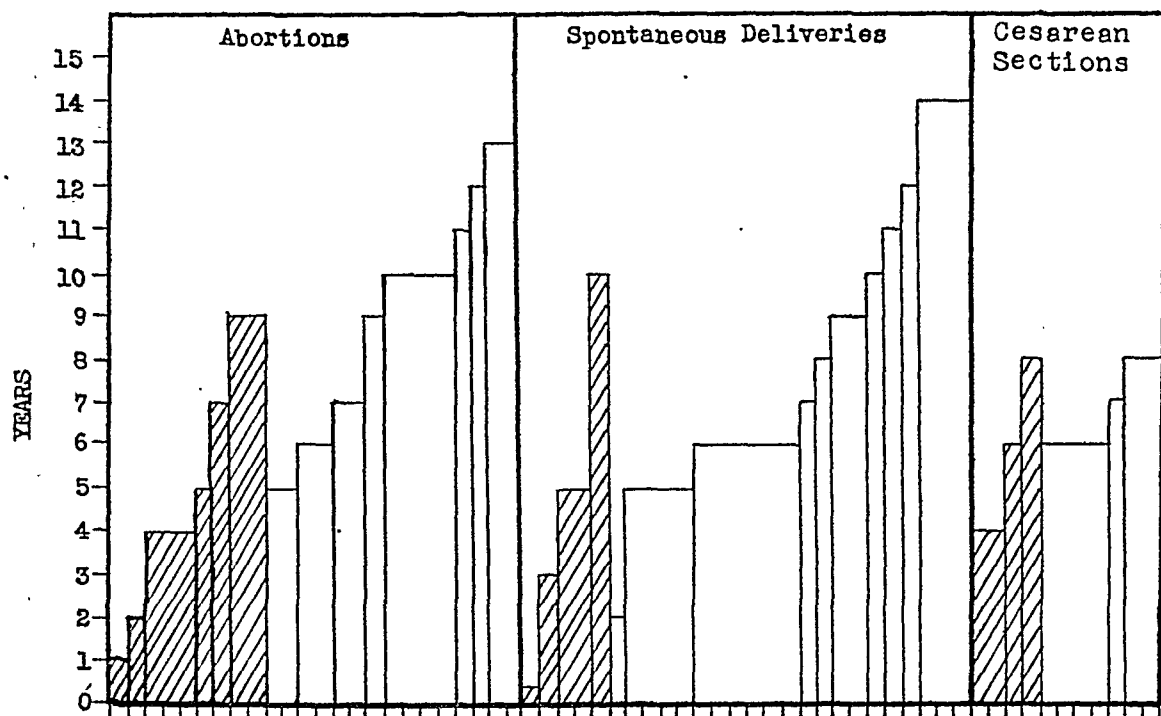


Fig. 1.—Length of study of the various patients in the survey. The mortality is represented by the shaded portions in the chart. Twenty-five patients were aborted; there were nine deaths. There were 26 spontaneous deliveries with five deaths; one patient is listed whose prognosis is poor. There were 11 cesarean sections, with four deaths. One patient was not included in this chart because of death due to a postoperative complication during a thoracoplasty operation. One patient, though followed for ten years, died of a syphilitic infection and has not been included in the final mortality figures. Only deaths directly due to tuberculosis were considered in the final results.

CASE 1.—D. S., a gravida ii, 25 years of age, white, was admitted to the hospital Aug. 15, 1937, with a pregnancy at term and a diagnosis of quiescent tuberculosis. She was delivered spontaneously, and her postpartum course was uneventful. Her tuberculosis was diagnosed as moderately advanced in 1931. She was admitted to the sanatorium at that time for stabilization of her pneumothorax and phrenectomy. The pneumothorax therapy was discontinued in 1932 because of an obliterative pleurisy. At that time the tuberculosis was considered as far advanced. On Jan. 29, 1934, the patient was readmitted and a thoracoplasty was done; the patient was discharged Nov. 24, 1934. A tonsillectomy was done in 1935. The patient became pregnant in 1936 and gave birth spontaneously to a term infant that same year. The following year she again became pregnant and was delivered spontaneously. Six months later (Feb. 17, 1938) her condition was considered as good, and on x-ray examination there was almost complete collapse of the left lung; her sputum was negative. She again became pregnant, and on Jan. 15, 1939, she was delivered by low cervical cesarean

Acute Active Tuberculosis

There was one patient diagnosed as having acute active tuberculosis. She died one year later following a therapeutic abortion and sterilization.

Case 4.—I. W., a gravida iii, 23 years of age, white, was admitted March 1, 1935, with a diagnosis of acute active tuberculosis. She was three months' pregnant, and the tuberculosis had been diagnosed during this pregnancy. Her previous two pregnancies were term, spontaneous deliveries—the last of which terminated three years before the present pregnancy. The pregnancy was terminated and the patient sterilized, and she was discharged March 28, 1935. She was immediately admitted to the sanatorium and died July 25, 1936.

Unilateral Moderately Advanced Tuberculosis

One patient had unilateral moderately advanced pulmonary tuberculosis. She was a gravida ii. The first pregnancy terminated spontaneously at term and occurred before the diagnosis of tuberculosis. A diagnosis of tuberculosis was made the following year, and three years later it was described by x-ray as advanced active tuberculosis. A thoracoplasty was done at that time. Two years later the patient again became pregnant. The pregnancy was terminated within the first trimester by x-ray induction which resulted in eventual sterilization. At the time of her second pregnancy there was marked fibrosis of the collapsed lung with no extension to the left lung.

Bilateral Moderately Advanced Tuberculosis

There were 19 patients in this group. Five patients were primiparas, and the remaining 14 were multiparas. The mortality was 26.4 per cent (five patients). In six patients the pregnancy was terminated in the first trimester by surgical means; in one patient the pregnancy was terminated in the first trimester but she was not sterilized. Three patients were delivered by cesarean section and the remaining nine were delivered spontaneously, of which one was sterilized on the tenth postpartum day.

One primipara had a complicating pre-eclampsia. Her membranes were ruptured artificially in the eighth month of pregnancy, and she was delivered spontaneously after a short labor. Her tuberculosis had been diagnosed three years previously. Following the diagnosis of tuberculosis the patient was hospitalized for six months. She received a total of eight months of pneumothorax therapy. The second primipara had a multiple pregnancy. She was delivered prematurely of viable twins at seven one-half months. She was then sterilized on the tenth postpartum day. Her tuberculosis had been diagnosed one year before her pregnancy. The third primipara was aborted and sterilized. Her tuberculosis had been diagnosed a few months before her pregnancy. The remaining two primiparas were aborted and sterilized. All five patients are living and well six to thirteen years after their last pregnancy, and on routine examination the tuberculosis was described as arrested.

In two of the five multiparas that died, pregnancy was terminated and sterilization done within the first trimester. They each had had one to four term spontaneous deliveries before the diagnosis of tuberculosis had been made.

Five of the six multiparas are living and well, and on last routine examination there was no evidence of tuberculous activity. The sixth patient was a gravida iii. Two term pregnancies had occurred before the diagnosis of tuberculosis: The third pregnancy was a spontaneous aseptic abortion at three months' gestation. Two years after this abortion the patient was bedfast with miliary tuberculosis and died the following year. Of the five multiparas that are living, one was delivered by cesarean section because of a pelvic deformity. A diagnosis of tuberculosis of the right hip was made thirteen years before. One year after her pregnancy there was minimal tuberculosis in her right lung. Six years later the patient had no evident active tuberculosis, and in this interval she again gave birth to a term infant by cesarean section. Termination of the pregnancy within the first trimester was done in three of the remaining four multiparas. Two of these patients had one or more term pregnancies before the diagnosis of tuberculosis. In one patient the diagnosis was made during her last pregnancy; in the other, the diagnosis of tuberculosis was made after her second pregnancy, and she received one year of pneumothorax therapy before her third and last pregnancy. The third patient had two spontaneous aseptic abortions before the diagnosis of tuberculosis was made and two abortions followed. The fourth multipara had three term spontaneous deliveries. The last pregnancy occurred after the diagnosis of tuberculosis. Four to ten years after their last pregnancy all four multiparas showed no evidence of tuberculous activity.

Moderately Advanced Inactive Tuberculosis

Two patients had moderately advanced inactive tuberculosis. One patient died of probable intestinal tuberculosis. No autopsy was obtainable.

CASE 3.—L. L., a gravida ii, 27 years of age, Negro, was admitted to the hospital Oct. 25, 1940, with a diagnosis of inactive moderately advanced tuberculosis and a pregnancy at term. She was delivered spontaneously. Early in her postpartum period she developed a febrile course with a temperature as high as 104° F. The patient had no respiratory signs or symptoms. On Dec. 6, 1940, the patient developed large cervical nodes which were proved to be tuberculous in origin. The patient was admitted to the sanatorium Dec. 15, 1940, and was discharged nine months later. At no time was there a positive sputum or evidence of tuberculous activity in the chest. On re-examination June 13, 1943, three years later, there were suggestive findings in the chest of active tuberculosis. When seen 10 months later the patient was gaining weight and doing well. On June 15, 1945, the patient complained of persistent diarrhea and had lost considerable weight. There was no significant tuberculosis in the chest, and the sputum was negative. The patient died three months later of probable intestinal tuberculosis.

Reactivation of a latent tuberculous process is very suggestive in this case because of the febrile postpartum course and the enlarged cervical nodes. The disappearance of the tuberculous process for approximately five years accounts for the probable diagnosis of intestinal tuberculosis for the cause of death which was suggestive by the clinical symptoms of diarrhea and marked loss in weight.

three years after the diagnosis of tuberculosis had been made. Seven years later she was diagnosed as having moderately advanced tuberculosis of the fibroid type. The fourth patient was diagnosed as having far-advanced tuberculosis five years after her last delivery. She was a gravida viii and seven pregnancies had occurred before the diagnosis of tuberculosis. Her husband had died four months before the termination of her last pregnancy of far-advanced active pulmonary tuberculosis. The fifth patient was a gravida v. She was delivered spontaneously at term. She had had three term pregnancies previous to the diagnosis of tuberculosis. Eight years later she was diagnosed as having quiescent moderately advanced tuberculosis of the fibroid type. The sixth patient was delivered spontaneously. Three term pregnancies had occurred before the diagnosis of tuberculosis and three term pregnancies followed. Upon re-examination fourteen years after the diagnosis of tuberculosis, tuberculosis of the cirrhotic type was found. The following year the patient was readmitted to the sanatorium for further treatment. The seventh patient was delivered by cesarean section three years after the diagnosis of tuberculosis. One term pregnancy had occurred five years before this diagnosis. One year following the cesarean section and sterilization the patient again became pregnant and the pregnancy was terminated within the first trimester of gestation and she was resterilized. Ten years later the prognosis was still guarded and the patient is on a limited routine. The eighth patient was a gravida iv. Tuberculosis was diagnosed a few months after her third spontaneous delivery. Her last pregnancy was terminated within the first trimester. At present the prognosis is still guarded and the patient rests two hours daily. The case history of the ninth multipara is presented.

CASE 6.—M. K., a gravida ii, 23 years of age, white, was admitted Jan. 7, 1940, with a diagnosis of tuberculosis moderately advanced, prognosis guarded, and inevitable abortion. In 1933 the right kidney had been removed because of tuberculosis. On Feb. 16, 1939, she was diagnosed as having pleurisy with effusion, and on x-ray examination there was tuberculous involvement of the right lung base. The patient became pregnant and the pregnancy was terminated at three months; her postoperative course being complicated by pneumonia and pleurisy. The patient was discharged Jan. 20, 1940, following a febrile postpartum course. This was followed by a gradual loss in weight and malaise. On x-ray examination, May 24, 1940, there was evidence of right upper tuberculosis with extensive pleuritis and fibrosis. On Jan. 17, 1941, the patient was again diagnosed as pregnant and a therapeutic abortion was done. On Feb. 6, 1942, the patient complained of a persistent cough and there were extensive fine râles in the left apex; she was advised not to become pregnant. On May 15, 1942, she was again diagnosed as three months pregnant and on x-ray examination there were small areas of involvement in the right apex and base. On x-ray examination Oct. 20, 1942, there was central cavitation with extensive hilar involvement of the right lung. On Nov. 12, 1942, the patient was delivered spontaneously. The pregnancy was complicated by a breech presentation. On April 1, 1943, there were no signs or symptoms of active tuberculosis. The patient again became pregnant and miscarried Sept. 9, 1943. On Sept. 24, 1943, there were no signs or symptoms of active tuberculosis and on x-ray examination the tuberculosis was considered as stable. On Jan. 17, 1944, routine examination showed inactive disease. At present the tuberculosis is considered as arrested.

The multipara that had one term pregnancy before the diagnosis of tuberculosis developed tuberculous peritonitis seven years after her abortion and died within two years. The tuberculosis had been diagnosed shortly after her first pregnancy. The other multipara was found to have tuberculosis after her fourth spontaneous delivery had occurred. She received pneumothorax therapy but remained ambulatory. Three years later she again became pregnant, and this was terminated at three months' gestation. At the time of her abortion, the tuberculosis was considered as quiescent. Four years later the patient died of far-advanced tuberculosis. The third multipara, a gravida vii, was found to have tuberculosis during her last pregnancy. She was delivered spontaneously and died ten years later of far-advanced pulmonary tuberculosis. The fourth multipara was delivered by cesarean section and sterilized. Her first pregnancy was a spontaneous term delivery, and tuberculosis was diagnosed one year later. Two years after the diagnosis of tuberculosis the disease was considered as arrested. The following year she developed a positive sputum and was hospitalized for ten months. When discharged from the sanatorium the tuberculosis was again considered as arrested. The fifth patient died six years after the diagnosis of tuberculosis. Her case history is presented.

CASE 5.—G. B., a gravida iv, 36 years of age, white, was admitted to the hospital Aug. 26, 1940, with a diagnosis of moderately advanced active tuberculosis with a guarded prognosis and pregnancy at term. The tuberculosis was first diagnosed in 1939. On x-ray examination June 1, 1940, there was extensive bilateral involvement. The patient was seven months pregnant at the time. Cesarean section and sterilization were recommended. The patient delivered spontaneously and was discharged Sept. 5, 1940, after an uneventful postpartum course. On x-ray examination of the chest on Nov. 18, 1940, there was extensive bilateral involvement but to no greater extent than in the previous x-ray examination taken when the patient was seven months pregnant. On Oct. 10, 1942, the prognosis was poor; the patient was losing weight and complaining of generalized chest pain. An x-ray taken Jan. 7, 1944, showed extensive tuberculous cavitation, and six months later the patient was hospitalized. She died May 12, 1945, of far-advanced tuberculosis.

The diagnosis of tuberculosis in this last patient was made during her fourth pregnancy. X-ray examinations made four months following delivery showed no further extent of the disease. The tuberculosis gradually progressed over a period of five years, terminating in death.

The remaining nine multiparas are living. The first patient was a gravida viii. She was delivered spontaneously. Six term pregnancies had occurred before the diagnosis of tuberculosis was made. Her initial diagnosis was made eight months after her sixth pregnancy. Two years later, there was minimal chest activity present. In this interval she gave birth to one term infant. During the five years that followed she again gave birth to another term infant. On last report her tuberculosis was considered as inactive. The second patient had stationary bilateral tuberculosis two years after her last pregnancy. She was a gravida v with three term pregnancies occurring after the diagnosis of tuberculosis. The third patient was a gravida iii. All pregnancies occurred

of the caseopneumonic type five years later. Two years previous to her last pregnancy she was hospitalized for five months, at which time a phrenectomy was done. The third patient was delivered by cesarean section. She was a gravida ii. Both pregnancies occurred after the diagnosis of tuberculosis. The first pregnancy was a spontaneous birth. She died four years after her last delivery. Two of the remaining six multiparas are living and well ten to fourteen years after the diagnosis of tuberculosis. Both cases are presented.

CASE 8.—L. S., a gravida ii, 24 years old, Negro, was admitted July 12, 1933, with a diagnosis of bilateral moderately advanced tuberculosis with cavitation, prognosis poor. She was at term and was delivered spontaneously, and was discharged July 27, 1933. Her postpartum course was complicated by a low-grade temperature and secondary anemia. Her tuberculosis was diagnosed during this pregnancy. She refused sanatorial care and was next seen Sept. 18, 1935, at which time she was diagnosed as having advanced tuberculosis with large cavitations. On Oct. 31, 1941, she gave birth spontaneously to a term infant and was sterilized on the tenth postpartum day. On x-ray examination two months after the last delivery there was scattered bilateral tuberculosis of moderate density with extensive fibrosis. On re-examination of the chest March 11, 1943, there was extensive bilateral tuberculosis with moderate fibrosis. The sputum was negative. The fibrosis was much more marked on x-ray examination of the chest June 12, 1944. On March 5, 1945, there were occasional râles and no symptoms of tuberculosis. On last examination May 6, 1946, she had symptoms of activity as verified by routine examination.

CASE 9.—H. M., a gravida ii, 27 years old, white, was admitted to the hospital Dec. 25, 1936, with a diagnosis of bilateral tuberculosis with a poor prognosis, eclampsia, and eight months' pregnancy. She developed convulsions the day before admission. On admission her blood pressure was 168/120. There was a 4 plus albuminuria. Membranes were ruptured artificially Dec. 29, 1936, and five and one-half hours later she gave birth spontaneously to a viable infant. The day preceding delivery she developed a fibrinous pleurisy. She was discharged from the hospital Jan. 17, 1937. Her tuberculosis had been diagnosed in 1932. She was hospitalized for three years. On x-ray examination June 13, 1935, there was scattered involvement of the right second and third interspaces with gross left lung tuberculosis. On May 8, 1936, there was a gross effusion of the left side of the chest. She was diagnosed as pregnant Sept. 10, 1936, but refused to be aborted and sterilized. Bed rest was advised, and the pregnancy was to be terminated by cesarean section. Re-examination of her chest four months after delivery showed no further extension of the disease. Nov. 12, 1937, she was seen, and she complained of nervousness and marked loss of weight. Her basal metabolic rate was found to be plus 50. A subtotal thyroidectomy was done March 5, 1938. X-ray of her chest was taken Oct. 21, 1938, and showed marked fibrosis; her sputum was negative and she was gaining weight. On x-ray of her chest May 16, 1941, there was extensive old right upper tuberculosis with gross left lung tuberculosis and marked pleural thickening with mediastinal detrusion. On June 18, 1943, the x-ray findings were essentially the same; her basal metabolic rate had risen to plus 30. On her last examination May 9, 1945, there was marked cirrhotic involvement of the left lung. At present the patient is doing well and is on a limited routine.

One multipara that was aborted and sterilized died five years later during a thoracoplasty operation. Three term pregnancies had occurred before the diagnosis of tuberculosis. The remaining three multiparas are dead. Two were

Advanced Tuberculosis

Sixteen patients had advanced pulmonary tuberculosis or advanced tuberculosis with involvement of the larynx or pharynx. There were seven primiparas and nine multiparas in this group. Eleven patients are dead.

Eighty-five per cent of the patients in whom the pregnancies were terminated within the first trimester of gestation died, as compared to 62.5 per cent of the patients who went to term. If we compared the patients who delivered spontaneously with those delivered by cesarean section, four delivered spontaneously and two died, as compared to three out of four patients who were delivered by cesarean section.

Two primiparas were aborted and sterilized, and one delivered spontaneously. The first patient that was aborted and sterilized had far-advanced tuberculosis, the diagnosis being made one year before her pregnancy. She died seven years later. The second primipara was diagnosed as having advanced bilateral pulmonary tuberculosis with laryngeal and pharyngeal involvement. She became pregnant four years later and was aborted and sterilized, and died four years later. The third primipara delivered spontaneously. She had far-advanced pulmonary and renal tuberculosis which was diagnosed during her pregnancy and died three years later. The fourth primipara was delivered by cesarean section and sterilized. Her tuberculosis was diagnosed as moderately advanced four years before. Two years after the cesarean section the patient again became pregnant and the pregnancy was terminated within the first trimester and the patient was re-sterilized. She died of far-advanced tuberculosis five years later. The fifth patient delivered spontaneously and expired on the fifth postpartum day. Her case is presented.

CASE 7.—M. S., a gravida i, 19 years old, white, was admitted to the hospital July 3, 1935, with a diagnosis of far-advanced, active tuberculosis with laryngeal and pharyngeal involvement. She was seven months pregnant. One year before admission she began to lose weight, developed a cough, slight temperature, night sweats, and hemoptysis. During the first half of her pregnancy she became hoarse and had difficulty in swallowing. She gave birth prematurely to a seven months' stillborn infant after a short uncomplicated labor. There was a rapid generalized failure following delivery, and the patient expired on the fifth postpartum day.

The remaining two primiparas are on a limited routine nine and eleven years, respectively, after the diagnosis of tuberculosis. One patient became pregnant one year after the diagnosis of tuberculosis and she was delivered at term by cesarean section and sterilized. The pregnancy in the other patient occurred four years after the diagnosis of tuberculosis, and it was terminated within the first trimester and the patient was sterilized.

All nine multiparas had far-advanced pulmonary tuberculosis. Two patients had two to five pregnancies before the diagnosis of tuberculosis. In both of these patients the pregnancy was terminated within the first trimester and one was sterilized. One patient died nine years after her last pregnancy. The other patient was diagnosed as having moderately advanced bilateral tuberculosis

On first admission there were 24 primiparas. Thirty-seven per cent of these patients became pregnant for the second time or more; 11.2 per cent of the patients that had more than one pregnancy are dead; 13.3 per cent of the patients with only one pregnancy are dead.

Eight primiparas delivered spontaneously with a mortality of 22.2 per cent. Two primiparas were delivered by cesarean section with no mortality, and in nine patients therapeutic abortions were performed, with a mortality of 22.2 per cent. If we classify these primiparas according to the extent of the tuberculosis, 50 per cent of the patients that were delivered spontaneously had moderately advanced active or far-advanced active tuberculosis. Fifty per cent of the patients that were delivered by cesarean section are also in this same classification, and 77.5 per cent of the patients in whom therapeutic abortion had been performed had advanced or moderately advanced active pulmonary tuberculosis. It is also noted that the age group for the primiparas varied from nineteen to thirty-eight years, and the four patients who died were in the age group from nineteen to twenty-one years. This is the age group wherein the highest mortality in tuberculosis occurs. If we consider the management of the pregnancy in these four patients, two patients were aborted and the remaining two delivered spontaneously. The two who delivered spontaneously had far-advanced pulmonary tuberculosis complicated by either renal or laryngeal and pharyngeal tuberculosis. The two patients who were aborted had far-advanced tuberculosis or tuberculosis complicated by laryngeal or pharyngeal involvement.

Eighteen multiparas delivered spontaneously, with a mortality rate of 16.6 per cent. Nine patients delivered by cesarean section with a mortality of 44.7 per cent. In 16 patients the pregnancies were terminated within the first trimester, with a mortality of 50 per cent. If we classify the multiparas according to the extent of the disease, 66.6 per cent of the patients who were delivered spontaneously had bilateral moderately advanced or far-advanced active tuberculosis; 44.4 per cent of the patients who were delivered by cesarean section were also in the above classification, and 100 per cent of the patients are dead; 62.5 per cent of the patients in whom therapeutic abortions were performed also had bilateral advanced or moderately advanced active tuberculosis. The age group for the multiparas varied from 23 to 44 years of age, and more deaths occurred between the ages of 23 and 30 than between the ages of 31 and 45 years.

Summary and Conclusions

1. A review of 62 tuberculous patients with a complicating pregnancy is presented.
2. The known incidence of tuberculosis complicating pregnancy at the Elizabeth Steel Magee Hospital is 0.35 per cent.
3. The final gross mortality in this survey was 33.8 per cent, and the corrected final mortality was 30.6 per cent.
4. The mortality for the patients who delivered spontaneously was 19.2 per cent.

delivered by cesarean section and sterilized, and died four to eight years after their last pregnancies. The last patient was aborted and sterilized and died four years after the diagnosis of far-advanced tuberculosis. Two term spontaneous deliveries had occurred within this interval of time.

Tuberculosis With Death Due to Other Causes

One multipara had unilateral active tuberculosis complicated by tertiary syphilis. She was a gravida vi and all pregnancies occurred after the diagnosis of tuberculosis. She died ten years later of tertiary syphilis as determined by autopsy findings, and was therefore not included in the final mortalities.

Management of Pregnancy

The conservative management of the pregnancy consisted in allowing the patient to go to term and to deliver spontaneously. Her antepartum care was augmented by careful management of the tuberculosis. This consisted in sanatorial care when needed and closely supervised ambulatory treatment. Anesthesia during delivery was limited to nitrous-oxide and oxygen supplemented with a pudendal block or low spinal anesthesia. The second stage of labor was shortened by resorting to low forceps delivery. All laparotomies performed either for cesarean section delivery of the patient or to abort and sterilize the patient were done under spinal anesthesia.

Discussion

Clinical studies for a period of five to fifteen years were made in 62 patients. The gross mortality was 33.8 per cent (21 deaths). The corrected final mortality was 30.6 per cent. Two deaths were excluded because one death was due to tertiary syphilis and the other death was due to generalized collapse during the fourth stage of a thoracoplasty operation. The mortality for the primiparas was 21 per cent, and the mortality for the multiparas was 32.5 per cent. Twenty-six patients delivered spontaneously with a mortality of 19.2 per cent. There were 11 cesarean sections with a mortality of 36.3 per cent, and the mortality was 38.5 per cent in 25 patients in whom therapeutic abortions were performed. This variation in mortality impresses one in the assumption that operative interference is associated with the greatest mortality (Table I).

TABLE I. INCIDENCE OF ADVANCED DISEASE WITH MORTALITY BETWEEN VARIOUS TYPES OF DELIVERIES

| | ABORTED | SPONTANEOUS | CESAREANS |
|----------------------------------|---------|-------------|-----------|
| <i>Primiparas</i> | | | |
| Moderately or advanced active | 77.7% | 50.0% | 50.0% |
| Mortality | 28.6% | 50.0% | ----- |
| <i>Multiparas</i> | | | |
| Moderately or advanced active | 68.8% | 66.6% | 44.4% |
| Mortality | 63.6% | 25.0% | 100.0% |
| <i>Combined results—</i> | | | |
| <i>Primiparas and multiparas</i> | | | |
| Moderately or advanced active | 73.3% | 53.3% | 47.2% |
| Mortality | 43.1% | 37.5% | 50.0% |

The above results are based on the final analysis of the patients and not on first admissions.

DILUTE SOLUTION, CATHETER, CONTINUOUS SPINAL ANALGESIA FOR LABOR AND DELIVERY*

A Preliminary Report

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IN OCTOBER, 1944, the first dilute solution continuous spinal anesthetic for labor and delivery was administered by one of us (S. M. S.) using a malleable needle and a needle shield so that the patient could lie on her back in her own bed during labor. This work was reported in an earlier issue of this JOURNAL.¹

On the basis of the contribution which Tuohy² made in introducing a ureteral catheter into the subarachnoid for anesthetic purposes, it was decided to continue dilute solution spinal analgesia for labor and delivery utilizing the catheter rather than the malleable needle and shield. We observed that the catheter technique offered more advantages and permitted greater control than the needle shield method.

The dilute solution approach toward the control of pain during labor and delivery was investigated in order to overcome some of the complications of continuous caudal analgesia such as: increased operative forceps deliveries, toxic reactions to the mother and fetus due to large amounts of anesthetic drugs, the imminence of massive spinal anesthesia should the epidural solution suddenly find its way into the subarachnoid space, the necessity for constant observation of the parturient, difficulty in inserting the needle, and the potentiality of infection in an extensively contaminated area.³

Continuous spinal analgesia for labor and delivery has been utilized by others such as Hinebaugh and Lang, Ebner and Lull, and Hingson. These workers, however, did not use extremely dilute anesthetic solutions which exert neither a somatic sensory nor a motor effect; and further, they were unable to permit the patient to lie on her back because of the indwelling needle, and withdrew the needle before transporting the patient to the delivery room. This technique did not gain much popularity because of persistent unilateral analgesia, paralysis of motor nerves, the anesthetic solution ascending to undesirable heights in the subarachnoid space, causing the blood pressure to fall to shock levels, interfering with uterine contractions, and subsequently retarding the normal progress of labor.

We have overcome the complications of continuous caudal analgesia and the undesirable features of spinal analgesia, as used in the past, by injecting into

*Presented before the First Annual Staff Meeting of the South Baltimore General Hospital on Jan. 8, 1947.

5. The mortality for the patients who delivered by cesarean section was 36.3 per cent.

6. The mortality for the tuberculous patients in whom the pregnancy was terminated within the first trimester was 38.5 per cent.

7. Sixty-one and five tenths per cent of the 62 patients had moderately advanced or far-advanced active tuberculosis; 44.8 per cent of these patients are dead. This included all types of deliveries including therapeutic abortions.

8. The best results in this survey were obtained in those patients who were delivered spontaneously regardless of the extent of the tuberculosis.

9. To determine tuberculous activity, physical examination, laboratory studies, including blood sedimentation rates, and serial x-rays are necessary.

ureteral catheter. The tubing and catheter are then washed out with several c.c. of the anesthetic solution in order to remove any autoclave debris, and is then laid aside.

A 2 c.c. Luer Lok syringe is then filled with 4 mg. or 0.4 c.c. of 1 per cent pontocaine. This is diluted to 2 c.c. with 10 per cent glucose omitting the adrenalin. A broken needle hub with solder at one end (called a nubbin) is locked onto the syringe tip in order to maintain the sterility of the contents. This is laid aside (Fig. 1).

The patient's back is then given a meticulous surgical preparation. A skin wheal is made with any suitable local anesthetic followed by $\frac{1}{2}$ c.c. of methedrine or any favorite vasoconstrictor except adrenalin. The vasoconstrictor is prophylactic against a reflex fall in blood pressure which some individuals might experience only on the initial injection. Additional doses of a vasoconstrictor are unnecessary with subsequent intrathecal injections.

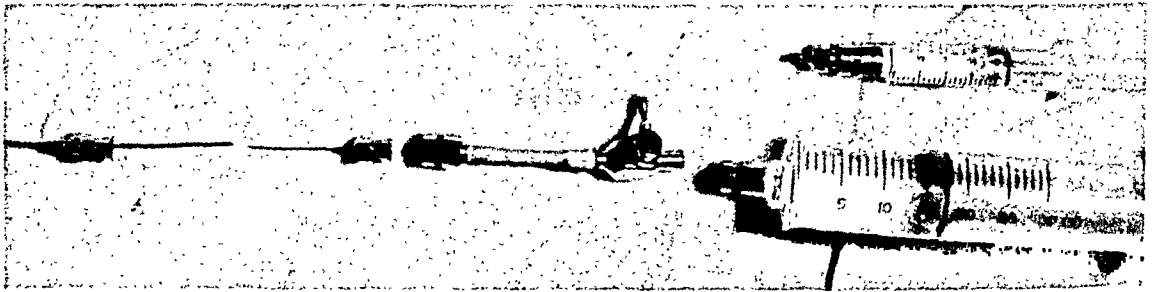


Fig. 1.—Assembly of continuous spinal equipment. The 2 c.c. syringe contains the concentrated solution with nubbin attached to tip. The 30 c.c. syringe contains the dilute solution. Stopcock attached to 2-inch piece of rubber tubing with Luer connection No. 608 L (Becton-Dickenson) at opposite end.

The 16-gauge special directional spinal needle is then inserted between the third and fourth lumbar vertebrae into the subarachnoid space. The needle is turned so that its aperture is directed cephalically, and the stilet is removed for a second, then replaced to determine whether spinal fluid is flowing freely. The catheter attached to the syringe is then picked up, the stilet again removed, and the catheter is inserted through the needle, carefully directing it cephalically into the subarachnoid space for about one inch so that its tip lies at the lower border of the second lumbar vertebra. The catheter is not inserted beyond this point so that the cord substance will at no time be contacted by the catheter. The needle is then gently withdrawn over the catheter, completely out of the back, and brought to the opposite end of the catheter (Fig. 2). *It is essential that the catheter never be pulled back through the needle once it has passed through the needle tip, since the catheter may be shorn off in the subarachnoid space by the sharp needle edge.*

The catheter is then bent over a $\frac{1}{2}$ -inch roll of sterile gauze and adhesived securely to the back (Fig. 2). If the gauze roll is not used the catheter tends to weaken because of the acute 90° angle made by the bend.

The patient is then asked to turn onto her back, elevating her head on a pillow (Fig. 3). The first injection consisting of 1 c.c., or $\frac{1}{2}$ mg., is made, providing the cervix is not fully dilated, by exerting considerable force on the plunger. This causes the small quantity of solution to shoot up the canal past the lumbar nerves to the vicinity of the eleventh and twelfth thoracic nerves. If the solution should travel beyond this point it would become so diluted in the spinal fluid that its effect would be completely dissipated by the time it reached the fifth or sixth thoracic segments. This implies that uterine

the subarachnoid space through a ureteral catheter an anesthetic solution which is so dilute that *no somatic sensory effect could be detected, and little or no motor paralysis involving the musculature of the thorax, abdomen, or extremities was produced; yet, the pain of labor contractions were abolished.*

Pains from the contracting uterus have been successfully abolished with solutions of pontocaine in glucose diluted to 0.05 per cent wherein $\frac{1}{2}$ mg. per c.c. was injected approximately once an hour. Patients were able to lie in any position desired, and could freely move about in bed, transfer themselves to the litter and onto the delivery table without experiencing the painful cramp of uterine contractions.

The special afferent sensory autonomic pathways conveying the sensation of pain due to contraction of the upper uterine segment was shown by Cleland⁴ to enter the cord through the sympathetic divisions of the 11th and 12th thoracic nerves. The pains caused by the contracting uterus before it becomes fully dilated can be completely controlled by injecting approximately $\frac{1}{2}$ mg. of pontocaine per c.c. per hour. The pain caused by distention of the birth canal, and the fully dilated cervix is experienced as a severe backache, or a sharp almost constant pain in the thigh, rectum, and sometimes the lower abdomen over the region of the bladder. This type of pain reaches its zenith when the cervix is fully dilated, and is conveyed to the central nervous system partly via the sacral parasympathetics, and partly through the sacral and lumbar somatic nerves. This type of pain will not be completely relieved with the extremely dilute solution of $\frac{1}{2}$ mg. or 1 c.c. per hour. It then becomes necessary to inject 1 to $1\frac{1}{2}$ mg. or 2 to 3 c.c. of the dilute solution before adequate relief is obtained. By injecting these quantities at one time some but not all motor control of the extremities is lost, with only slight change in the tone of perineal musculature.

For the actual delivery the dilute solution syringe is removed and a syringe containing 4 mg. of pontocaine in glucose is substituted and injected slowly with the patient in reverse Trendelenburg position. This will completely abolish the sensation of pain, stretch, pulling, or any other discomfort caused by either spontaneous or forceps delivery, and at the same time institute profound relaxation of the perineum and birth canal. The ureteral catheter and a hyperbaric anesthetic solution make these segmental blocks both simple and possible.

Technique

The dilute anesthetic solution is mixed as follows:

Into a 20 or 30 c.c. Luer Lok syringe 1 c.c. or 10 mg. of 1 per cent pontocaine solution is aspirated. Glucose 10 per cent is then aspirated to the 20 c.c. mark. In order to prolong the action of the anesthetic $\frac{1}{4}$ c.c. of adrenalin 1:1000 is added to the solution.

The syringe is then attached to a stopcock which, in turn, is connected to a 2-inch piece of high pressure continuous spinal rubber tubing which contains a Luer connection at its opposite end (Fig. 1). This Luer connection is then locked to the 23 gauge needle which projects out of the end of the No. 3

to control the pain. It then becomes necessary to inject 2 or 3 c.c. or make a slightly more concentrated solution by adding 1 mg. of pontocaine solution to each c.c. rather than $\frac{1}{2}$ mg. and injecting 1 or 2 c.c. of this. Injections to terminate the pains associated with a fully dilated cervix are made very slowly with the patient in a slight sitting position which permits the solution to fall caudally and contact the lower lumbar and sacral nerves. If "bearing down" is desired, the patient can be instructed to use her abdominal muscles synchronously with the uterine contractions since there is no muscle paralysis at this stage of the anesthetic.

When the decision is made to deliver the fetus, following a sterile vaginal examination on the delivery table in order to confirm the rectal diagnosis, the table is placed in reverse Trendelenburg position. The 2 c.c. syringe containing the 4 mg. of pontocaine in 2 c.c. of glucose is attached to the 23 gauge needle projecting from the catheter, after disconnecting the larger syringe. The solution is injected so slowly that fully two minutes should be required to inject the contents of the syringe. When the syringe is empty one minute more is allowed to elapse, after which the table may be levelled. This injection may be made while the patient is up in stirrups and completely draped. The slowness of the injection causes the hyperbaric solution to "fall" caudally in a bulk and exert its effect primarily on the sacral and lower lumbar nerves. This injection relieves all pain from vaginal, perineal, and cervical distention, and produces complete relaxation permitting episiotomy, forceps application if necessary, or any type of operative procedure required. It will produce anesthesia from one and one-half to two hours, and, because it is primarily a saddle block, the patient will be able to move her lower extremities to a certain extent.

After delivery room procedures are completed the patient is positioned as for administering the spinal and the catheter is gently and slowly removed. A sterile, antiseptic dressing is then placed over the needle area.

In general, analgesia is begun in nulliparas when the cervix is 6 to 7 cm. dilated, and in multiparas when 3 to 5 cm. dilated; the presenting part must be engaged and at least on a level with the ischial spines. If a nullipara is particularly uncomfortable before progressing to the specified dilatation, small doses of demerol or seconal are administered without scopolamine or paraldehyde since it is important to maintain a rational and cooperative patient at all times. As Hingson has stressed in his work with continuous caudal analgesia, the method was designed to relieve the pains and not the early discomforts of labor.

This type of analgesia, as with continuous caudal, is not recommended in cases of contracted pelvis, bleeding, syphilis, or tumors of the central nervous system, local infection at the site of injection, in the presence of a floating, unengaged fetal head.

Selected Case Histories

CASE 1.—A para 0-0-0-0, aged 19 years. Her antepartum course was uneventful. The initial injection of 1 c.c. or $\frac{1}{2}$ mg. was given at 11:30 A.M. when the patient was 7 cm. dilated, pains every three minutes, and the head at two below the spines. At 12:20 P.M. cervix was 8 to 9 cm. dilated. She was given another $\frac{1}{2}$ mg. At 1:55 P.M. the cervix was almost fully dilated and the head three below the spines, $\frac{1}{2}$ mg. given. At 3:20 P.M., the patient received her final concentrated injection of 2 c.c. or 4 mg. of pontocaine in glucose while in reverse Trendelenburg position on the delivery table. The table was levelled after one minute and a central episiotomy performed. Outlet forceps were applied, and a 7-pound male delivered in left occipitoanterior position without manual or

contractions will not be impeded since the autonomic motor fibers to the uterus leave the spinal cord in this region.

The initial injection will obtund all pain due to uterine contractions, but will not paralyze the musculature innervated by the nerves with which it comes in contact. However, it will only partially obliterate the low back,

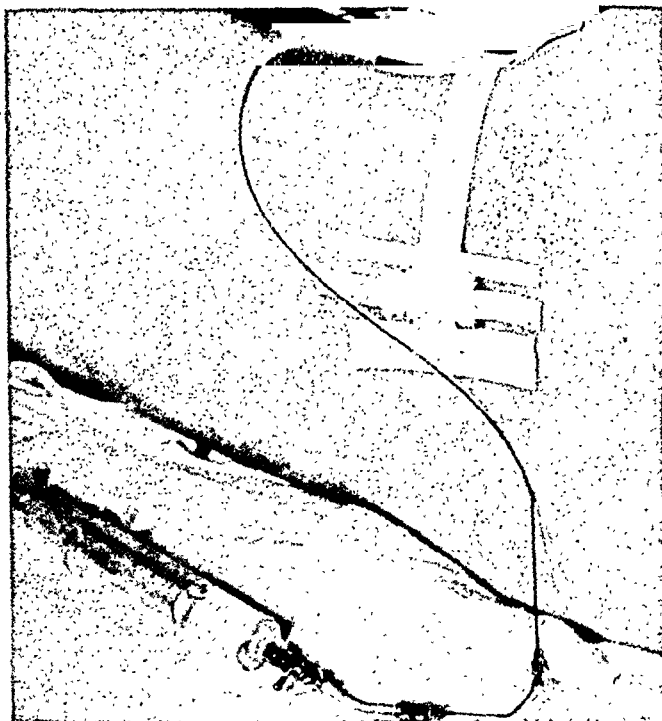


Fig. 2.—Number 3 ureteral catheter bent over roll of sterile gauze and adhesived to back. The 16 gauge needle has been withdrawn from subarachnoid space and lies at opposite end of catheter where it remains during labor and delivery.

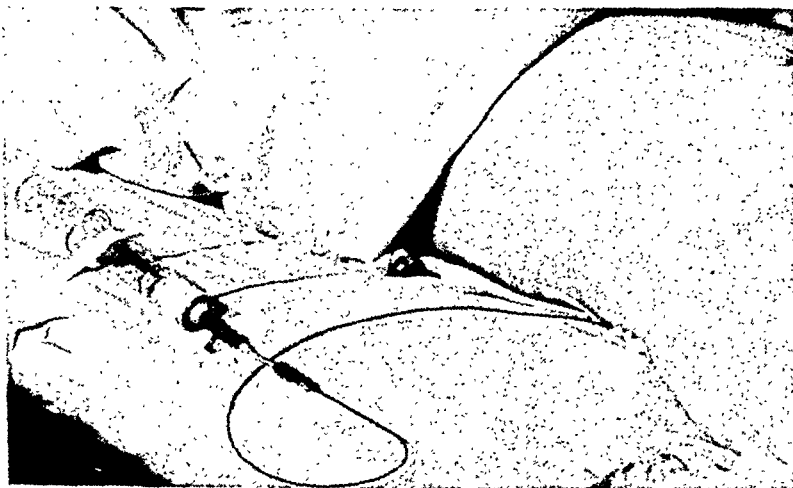


Fig. 3.—Patient well advanced in labor, lying on her back with dilute solution syringe adhesived to the bed. One c.c. or $\frac{1}{2}$ mg. of pontocaine is injected approximately every hour. She has full control over all her muscles.

thigh, and rectal pain caused by progressive cervical dilatation. These latter pains are lessened somewhat, and the patient is infinitely more comfortable than before the injection.

If the initial injection is made when the cervix is fully dilated, but the head is still level with the spines, the $\frac{1}{2}$ mg. or 1 c.c. dose will not be sufficient

BLE I

| PATIENT | AT START OF ANESTHETIC | | | DELIVERY POSITION | DURATION OF STAGES | | | DURATION OF ANESTHETIC | |
|---------|---------------------------|---------------|---------------------------------|-------------------|--------------------|--------------------|------|------------------------|--------------------|
| | PAIN INTERVALS IN MINUTES | CERVIX IN CM. | DESCENT A—ABOVE B—BELOW L—LEVEL | | POSITION | DURATION OF STAGES | | | H—HOURS M—MIN-UTES |
| | | | | | | M—MINUTES | 2ND | | |
| 36912 | 0000 | 7 | 1 B | LOA | E—F—LOA | 25½ H | 12 M | 1 M | 3 H |
| 20717 | 3003 | 4 | 1 A | LOT | E—MR—LOT to LOA—F | 12 H | 2 H | 3 M | 6 H |
| 24854 | 2000 | 7 | Level | LOT | S—LOA | 8½ H | 21 H | 4 M | 4 H |
| 36974 | 1000 | 8 | 2 B | LOA | F—LOA | 4½ H | 45 M | 5 M | 45 M |
| 36977 | 2002 | 10 | 2 B | ROA | F—ROA | 10 H | 30 M | 2 M | 45 M |
| 36990 | 0000 | 7 | 1 B | LOT | E—M—LOA | 42 H | 23 M | 2 M | 5 H |
| 37040 | 0000 | 7 | 2 B | ROA | E—M—ROA | 15 H | 50 M | 11 M | 6½ H |
| 37043 | 0100 | 7 | 1 B | ROA | E—F—ROA | 10 H | 35 M | 3 M | 6½ H |
| 37078 | 0000 | 10 | 2 B | LOT | E—MR—LOT to LOA—F | 6½ H | 42 M | 8 M | 2 H |
| 37095 | 0000 | 8 | 1 B | LOT | E—MR—LOT to LOA—F | 28 H | 35 M | 4 M | 5 H |
| 37113 | 0000 | 7 | 2 B | LOA | E—F—LOA | 20 H | 1½ H | 9 M | 4 H |
| 37102 | 0000 | 8 | Level | ROT | E—MR—ROT to ROA—F | 12 H | 45 M | 5 M | 3 H |
| 37044 | 0000 | 10 | Level | LOT | E—F—LOA | 17 H | 2½ H | 3 M | 3 H |
| 34309 | 2012 | 4 | Level | LOT | E—F—LOA | 16 H | 33 M | 2 M | 2 H |
| 17741 | 1001 | 9 | 2 B | LOA | S—LOA | 4½ H | 9 M | 4 M | 45 M |
| 37263 | 2002 | 5 | 2 B | ROA | S—ROA | 2½ H | 9 M | 1 M | 15 M |
| 35534 | 0000 | 5 | 1 A | LOA | E—F—LOA | 14 H | 24 M | 3 M | 3 H |
| 36588 | 0000 | 5 | 2 B | Level | S—(Monster) | 22 H | 57 M | 6 M | 9½ H |
| 34896 | 0000 | 5 | Level | ROT | E—FR—ROT to ROA—M | 10 H | 20 M | 35 M | 1 H |
| 23641 | 1001 | 5 | 1 B | LOA | S—LOA | 18 H | 1½ H | 10 M | 2 H |
| 37396 | 0000 | 8 | 2 B | ROT | E—F—LOA | 8 H | 45 M | 3 M | 2 H |
| 37513 | 0000 | 9 | 1 B | LOA | E—F—LOA | 17 H | 1½ H | 26 M | 3½ H |
| 37515 | 1001 | 4 | 1 A | LOA | E—F—LOA | 20 H | 45 M | 1 M | 4½ H |
| 30817 | 1001 | 3 | 2 B | ROA | E—F—ROA | 15 H | 24 M | 6 M | 3½ H |
| 37531 | 0000 | 5 | 1 B | ROT | E—F—ROA | 7 H | 39 M | 6 M | 4½ H |
| 33352 | 1001 | 6 | 2 A | ROT | E—F—ROP | 19 H | 52 M | 4 M | 3½ H |
| 36000 | 0000 | 4 | 1 A | ROA | S—ROA | 21 H | 40 M | 30 M | 10 H |
| 33012 | 7007 | 3 | 2 B | ROA | E—F—ROA | 22 H | 7 M | 5 M | 2 H |
| 36477 | 2001 | 5 | 1 B | LOA | S—LOA | 22 H | 57 M | 3 M | 25 M |
| 16092 | 1001 | 6 | 2 B | LOA | E—F—LOA | 6½ H | 58 M | 22 M | 1½ H |
| 36521 | 0000 | 9 | 2 B | LOA | E—F—LOA | 23 H | 51 M | 2 M | 1 H |
| 36539 | 0000 | 4 | 1 A | LOT | E—F—LOA | 19 H | 2 H | 20 M | 5½ M |
| 34202 | 2002 | 6 | Level | LOA | S—LOA | 13 H | 11 M | 4 M | 5½ M |
| 36559 | 0000 | 9 | 2 B | ROA | E—F—ROA | 11 H | 26 M | 1 M | 5½ M |
| 36571 | 4003 | 4 | 2 A | LOA | S—LOA | 17 H | 15 M | 5 M | 2½ H |
| 36579 | 0000 | 6 | 1 B | ROT | E—LOA (Twins) | 38 H | 46 M | 4 M | 27 H |
| 36584 | 0000 | 4 | 2 B | LOT | E—FR—ROT to ROA—M | 24 H | 3½ H | 1 M | 27 H |
| 36596 | 0000 | 5 | Level | LOT | E—F—LOA | 46 H | 2 H | 3 M | 8½ H |
| 36628 | 0000 | 5 | Level | LOT | E—MR—LOT to LOA—F | 18 H | 41 M | 4 M | 6 H |
| 36711 | 0000 | 5 | 1 B | LOA | E—F—LOA | 14 H | 18 M | 1 M | 2 H |
| 36758 | 1001 | 6 | 1 B | LOT | E—F—LOA | 5½ H | 39 M | 1 M | 2 H |
| 37575 | 2002 | 7 | 2 B | ROA | S—ROA | 5½ H | 51 M | 13 M | 1 H |

forceps rotation at 3:32 P.M. The child cried spontaneously. Blood loss was approximately 60 c.c. There were no postpartum complications. Patient asked if she could have her next baby in the same manner.

CASE 2.—A para 2-0-0-0, aged 23 years. Her antepartum course was uneventful. The initial injection of 2 c.c. or 1 mg. was given at 9:45 P.M. when the cervix was 7 cm. dilated. Membranes were intact, and the fetal head level with the spines. At 10:35 P.M. 1 mg. was injected when the cervix was fully dilated and the head below the spines. At 11:40 P.M. another mg. was given when two below the spines. Another mg. at 12:25 A.M., and another at 1:05 A.M. At 1:35 A.M. the final concentrated injection of 4 mg. in 2 c.c. of glucose was given with the patient in reverse Trendelenburg position. At 1:45 A.M. an 8-pound male was delivered spontaneously without episiotomy and repair. The baby cried immediately. Blood loss was about 50 c.c. The postpartum course was uneventful.

Results

Contrary to the majority of reports regarding continuous caudal analgesia, we have not experienced in the present series of fifty cases any increase in operative or midforceps interference as a result of the anesthesia. In several cases where the patient was making no progress after three or more hours of analgesia, further injections were discontinued with the catheter still remaining in place, while the normal pains were permitted to return. In these cases no further progress was made, even when the patient labored and experienced unabated pain. In one case a contracted pelvis existed; in another, unsuspected twins were present. Since each injection of 1 c.c. lasts approximately forty-five minutes to one hour, it is simple to permit the parturient to resume the cognizance of her contractions by discontinuing the analgesia with the catheter still in place.

There were no maternal or fetal deaths in the series. There were no cases exhibiting a fall in blood pressure; toxic reactions of any type either to mother or child; no cases requiring supplemental anesthesia such as cyclopropane, gas, or ether; no postpartum infections at the site of needle insertion; nor were there any postpartum backaches.

There were no neurological sequelae. Postspinal headaches were not increased over what one would expect in a similar series on fifty patients undergoing general surgery under spinal anesthesia. All patients were maintained in a horizontal position for at least twelve hours post partum either on the side, back, or abdomen, depending on the patient's desire.

There were no failures to enter the subarachnoid space or to insert the ureteral catheter, and no instances of needle or catheter breakage. Catheters were used only five times and in some cases less before being discarded.

It was our impression that the first stage of labor was not retarded; the second stage remained normal but was definitely not prolonged. The patient could at all times effectively "bear down" if desired, because abdominal musculature was not paralyzed. There was no delay in the normal progress of labor whether the position of the fetus was anterior, transverse, or posterior. The third stage was of normal duration with minimal blood loss. Babies did not require resuscitation.

Complications

There were no complications of any kind in this short series. However, the possibility of complications such as meningitis, backache, shorn off catheter tip, abducens nerve palsy, persistent cephalalgia, and other neurological sequelae must always be considered.

INDUCTION OF LABOR AT THE CHICAGO LYING-IN HOSPITAL*

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IF THE termination of pregnancy is indicated after thirty-two weeks, the doctor must choose either elective cesarean section or the induction of labor. The latter would be completed preferably by vaginal delivery and rarely by cesarean section. The artificial termination of pregnancy by any method is inevitably followed by an increased fetal and maternal morbidity and mortality. In a long experience of full-time obstetrics, we have seen a number of mothers and babies die as the result of induction. The maternal deaths were due to infection or to hemorrhage and shock. The babies die from prolonged labor, infection, injuries, or from prolapsed cord. Some of these mothers and babies would undoubtedly have died from the condition under treatment which was placenta previa, abruptio placenta, or toxemia, but a number were preventable deaths.

When the Chicago maternal deaths are discussed at the monthly meetings, there is usually at least one patient in whom labor was induced for toxemia or postmaturity. The death was due to: shock and hemorrhage resulting from forcible dilatation of the cervix; infection due to long ruptured membranes; or to peritonitis resulting from cesarean section after attempts at induction of labor. In most of these cases there was no real indication for the induction, and there were at least preventable factors. The outcome could have been no worse, and in all probability, would have been much better had the induction not been carried out.

The mystery that has always interested us is not why patients go into labor after injections of solution of posterior pituitary (hereafter abbreviated to "S.O.P.P.") or mechanical induction; but why the baby has remained in utero for some forty weeks despite the well-known fact that the uterus always expels its contents (blood clots, myomas, packs, and bags). Furthermore, those patients who do not go into labor after induction are an even greater mystery. Hormone changes are not the only cause. There must be some trigger mechanism which starts the uterus into normal labor. One of us has been constantly with patients who had strong painful uterine contractions at regular intervals for as long as twenty-four hours of either spontaneous onset or due to repeated injections of S.O.P.P. However, there was no change in the amount of dilatation or in the descent of the presenting part. The uterus contracted but did not retract, which is essential for the expulsion of its contents. There was a bag of forewaters in some of these patients, but the cervix did not dilate because there was no retraction of the uterine muscle. If the

*Read before the Chicago Gynecological Society, November 15, 1946.

Summary

By means of a ureteral catheter an extremely dilute solution of pontocaine in glucose is introduced into the subarachnoid space. It was demonstrated for the first time that a dilute solution of pontocaine which seems to possess no affinity for tactile, proprioceptive, thermal, pain, or motor nerves, does exert a selectivity for those nerves which convey the sensation experienced as pain from the contracting uterus without interfering with the intensity, duration, or interval of the contractions.

Since the patient retains complete skin sensation and motor tone during labor, it is necessary to substitute a more concentrated anesthetic solution just prior to the actual delivery. This is accomplished by an interchange of syringes at the distal end of the ureteral catheter, when the patient is on the delivery table and fully draped.

This approach toward the control of pain in childbirth eliminates the apprehension associated with the possibility of sudden, massive, high spinal anesthesia; hypotension due to loss of muscle tone, eliminates the necessity for constant observation of the patient, permits the patient greater freedom of movement, and removes the point of catheter insertion from the area of rectal contamination.

We feel that this new approach is a safe, practical procedure possessing many advantages over continuous caudal analgesia. Its proper niche in the field of obstetric pain relief still remains to be evaluated.

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Table I lists the methods used by us for inducing labor. We have arranged the indications according to our idea of their importance.

TABLE I. INDICATIONS AND METHODS FOR INDUCTION OF LABOR

| INDICATION | S.O.P.P. AND PITSULFONATE | | | | RUPTURED MEMBRANES | | | | R.M. AND TRACTION OR BAG AND S.O.P.P. | |
|---------------------------|------------------------------|----|------------|----|-----------------------|----|----------|----|--|-------|
| | P. | M. | AFTER R.M. | | P. | M. | S.O.P.P. | | P. | M. |
| | | | P. | M. | | | P. | M. | | |
| Placenta previa | 1 | 1 | 1 | 1 | 3 | 7 | | 4 | | 4 |
| Abruptio placenta | | | | | | 2 | | | | |
| Eclampsia | | | | | 2 | 1 | | 1 | | 1 |
| Nonconvulsive toxemia | 8 | 8 | 6 | 1 | 9 | 9 | 2 | 4 | 3 | 1 |
| Systemic disease | | 1 | 2 | 1 | 1 | 1 | | 3 | | |
| Postmaturity | 3 | 11 | | | 2 | 3 | 2 | 2 | | |
| Polyhydramnios | | 1 | | 1 | 4 | 4 | | 1 | | |
| Miscellaneous (R.M. etc.) | 5 | 26 | 43 | 61 | 3 | 8 | 4 | 1 | | 2 |
| Total number | 17 | 48 | 52 | 65 | 24 | 35 | 8 | 16 | 3 | 8=276 |

P = primipara; M = multipara; R.M. = ruptured membranes; S.O.P.P. = solution of posterior pituitary.

Placenta Previa.—If there is some cervical dilatation and if the previa is not a total one, we rupture the membranes. If the bleeding cannot be controlled by rupture of the membranes with traction on the head or on the foot, we perform a cesarean section. We rarely use the bag or pack.

Abruptio Placenta.—We rupture the membranes and usually these patients deliver very rapidly. During this period the patient is given adequate amounts of blood, and parenteral glucose and saline solutions. If the patient shows clinical improvement, nothing else is done. If, at the end of four to eight hours, there has been no change in the cervix and the patient on admission had presented evidence of great blood loss (indicative of complete separation and/or a Couvelaire type uterus), the case is again evaluated and a cesarean section may be performed.

Eclampsia.—After the patient has been treated medically, which requires four to six hours, a vaginal examination is made and if there is any dilatation, the membranes are ruptured. Occasionally, a bag may be introduced to hasten delivery.

Nonconvulsive Toxemia.—No one will debate but what the best treatment for toxemia is termination of the pregnancy. However, in many of the patients, the toxemia is of such a degree that the pregnancy can be permitted to continue until the baby is near term or until the cervix is ripe. Certainly, severe toxemia at any time and especially after thirty-two weeks warrants termination of the pregnancy. Our practice for many years has been to evaluate the seriousness of the toxemia and its effects on both maternal and fetal life. When the toxemic patient is two to four weeks before delivery it is amazing how much change can occur in the cervix in seven to ten days' time.

From 1931 to 1936, 21 per cent of our toxemic patients were induced and 21 per cent had an abdominal delivery, a total of 42 per cent. By 1939, these figures were 14 and 9 per cent, respectively. Our fetal and maternal mortality in some 300 toxemic patients per year has been steadily decreasing primarily because of earlier recognition and treatment of the toxemia while it is still mild.

Systemic Disease.—Certain cardiac patients who have been hospitalized, are compensated and in whom the cervix is ripe, usually have labor induced by rupture of the membranes. These patients should not be permitted to carry the baby any longer than is necessary. Furthermore, induction of labor permits the optimum time to be selected. Patients with pulmonary tuberculosis, severe anemia, or diabetes mellitus, should be induced, in general, when the cervix is ripe.

doctor did not recognize the false labor, he would rupture membranes or insert a bag. The usual result was a long labor, a difficult delivery, uterine sepsis, and frequently a dead or injured baby. If he sent these patients home, they would come back days, or even weeks later and then have a normal labor.

Overdistention of the uterus by twins or by polyhydramnios results in premature labor, but comparable or even greater distention by a single baby whose volume may be more than that of either of the other conditions, does not result in premature labor.

The senior author during the period 1921 to 1927 had an extensive experience with induction of labor when it was used in the treatment of especially postmaturity and contracted pelvises. A high fetal and maternal morbidity and mortality resulted, and we discontinued treating these conditions by induction. The staff at The Chicago Lying-in Hospital also induced labor for similar indications, but since 1933 we have been constantly decreasing the number of inductions by a better evaluation of the indication and a better selection of the optimum time. We are guided by the condition of the cervix.

During the thirty months ending June 30, 1943, there were 8,503 deliveries and 618 attempted inductions of labor, an incidence of 7.3 per cent. There were 136 failures with castor oil and quinine which are not included; 20 with S.O.P.P.; four after rupture of membranes; and one after rupture of membranes, traction on bag and S.O.P.P. One hundred eighty-three histories were deleted because although delivery occurred, the latent period after rupture of the membranes was less than one hour or longer than 12 hours after injections of S.O.P.P. Thus 276 patients, 3.2 per cent, had an induction of labor and 342 patients, 4 per cent, had a cesarean section; or a total of 616, 7.3 per cent, of our patients had the pregnancy artificially terminated. The incidence of failure was 9 per cent.

The reports¹ published since 1930 demonstrate that although there has been a decrease in the fetal and maternal mortality due to induction of labor, it is still a significant figure. The uncorrected fetal mortality ranges from 0 to 37 per cent, and the maternal from 0 to 2.8 per cent. The corrected mortality figures are much less, but still as a rule higher than the normal percentages. Browne² reported that 5 per cent of 173 maternal deaths in nine British maternity hospitals staffed by experts, followed directly on induction. The figures for maternal morbidity are 3 to 25 per cent. Since the average morbidity in most maternity hospitals is 7 to 10 per cent, it is obvious that the morbidity is increased with its inevitable residual damage from puerperal infection. The number of failures to initiate labor ranged from 0 to 30 per cent.

Gillett,³ in 1944, reported a thousand consecutive inductions of labor without any failures. Labor began in all cases within twelve hours. There were no maternal deaths and no stillbirths. There were eight neonatal deaths none of which were attributable to the induction. Even though all the cases were very carefully selected, this is an unusual record.

Induction of labor is indicated in comparatively few cases as compared to twenty-five or more years ago when the cesarean section mortality was 10 per cent or more. *The primary indication must always be, is the patient better off with the uterus empty; or if the infant is alive and in good condition, is its chances of survival increased by early delivery.*

Cesarean section was performed in five patients who did not go into labor as a result of either S.O.P.P. and rupture of the membrane or the additional use of volsellum in two cases (cesarean-hysterectomy). There were definite indications for the operations in all cases; placenta previa in two cases and disproportion in three cases.

There were two maternal deaths, one patient had an abruptio placenta and at autopsy also had a cortical necrosis of the kidney, necrosis of the anterior lobe of the pituitary, and an eclamptic liver. Obviously the rupture of the membranes was not a factor. The other patient had been observed for some weeks and in view of the increasing severity of the toxemia it was deemed advisable to induce labor. The baby died in utero, the bag was expelled, and the uterus was ruptured by an inexperienced resident attempting to deliver an impacted shoulder in a baby weighing 1,600 grams. The death in this case was related in part to the induction.

There were 17 fetal deaths, but 4 of these weighed less than 1,500 grams. Three of the deaths were ante partum, two intra partum (one from prolapse of the cord), two from major anomalies, one from toxemia, three from previa, and two from abruptio. A corrected fetal mortality is 0.7 per cent.

Our average hospital morbidity is 9 per cent. The morbidity in patients who were induced was 14.7 per cent (38 to 38.9° C.); 4.7 per cent (39° C.+) a total of 19.4 per cent. There was only one serious case of pelvic thrombophlebitis (placenta previa). Eight patients had pyelitis, three mastitis, three respiratory infections, and one an infected episiotomy.

Table II lists the duration of the latent period and of labor for the various methods of induction. We have mentioned that many of these cases have already been deleted because the latent period was less than one hour. Since labor began within less than six hours in 65 to 91 per cent of the cases, it is obvious that the patients had been carefully selected for induction.

TABLE II. DURATION OF LATENT PERIOD AND OF LABOR

| METHOD OF INDUCTION | HOURS | | | | |
|---|-------------------------|-------------------------|--------------------------|---------------------------|---------------------------|
| | 1 TO 2 (PER CENT) | 2 TO 6 (PER CENT) | 6 TO 12 (PER CENT) | 12 TO 24 (PER CENT) | 24 TO 80 (PER CENT) |
| S.O.P.P. or Pitsulfonate | | | | | |
| Primipara—Latent period | 67 | 4 | | 12 | 17 |
| —Labor | 3 | 28 | 25 | 25 | 19 |
| Multipara—Latent period | 75 | 9 | 11 | 5 | |
| —Labor | 26 | 51 | 15 | 8 | |
| S.O.P.P. or Pitsulfonate after Spontaneous R. M. | | | | | |
| Primipara—Latent period | 78 | 6 | 6 | 2 | 8 |
| —Labor | 3 | 26 | 43 | 26 | 2 |
| Multipara—Latent period | 81 | 10 | 3 | 2 | 4 |
| —Labor | 14 | 51 | 22 | 12 | 1 |
| Rupture Membranes | | | | | |
| Primipara—Latent period | 21 | 54 | 4 | 17 | 4 |
| —Labor | | 35 | 30 | 22 | 13 |
| Multipara—Latent period | 32 | 34 | 20 | 12 | 2 |
| —Labor | 3 | 65 | 24 | 8 | |
| R.M. and S.O.P.P. | | | | | |
| Primipara—Latent period | (50) | | 33 | 17 | |
| —Labor | | (17) | 50 | 33 | |
| Multipara—Latent period | 26 | | 16 | 42 | 16 |
| —Labor | | 37 | 42 | 21 | |

() = less than 10 patients.

Habitual Intrauterine Fetal Death.—The pregnancy is terminated at thirty-five to thirty-seven weeks by cesarean section or by induction if the cervix is ripe.

Polyhydramnios.—When the distention of the uterus causes cardiac and/or respiratory embarrassment, the membranes are ruptured. We have aspirated amniotic fluid through the abdominal wall but many of these babies are abnormal and nothing is gained by continuing the pregnancy. An x-ray should be obtained as soon as the fluid has been drained off and frequently an abnormal fetus can be detected.

Twin Pregnancy.—Because of the overdistention even though there may be 3 or more centimeters of cervical dilatation, the uterus may not contract. Rupture of the membranes, permitting as much fluid as possible to escape, will usually precipitate labor.

Convenience.—In general, induction of labor should not be carried out for the convenience of either doctor or patient. Three patients were induced for the doctors' convenience. Twelve multiparous patients who lived a considerable distance from the hospital were sent in for rupture of the membranes when the cervix was ripe. This is proper obstetrics.

Ruptured Membranes.—Patients with ruptured membranes are examined vaginally. If the cervix is ripe, they are given fractional doses of S.O.P.P., according to our routine. S.O.P.P. is not given after the membranes have been ruptured for twenty-four or more hours because of the increased likelihood of uterine rupture. If the cervix is closed, or if there is a long canal, no further measures are carried out. The patient is sent to her room, permitted to be up and about, vaginal instillations of 1 per cent merthiolate in glycerin are made every twelve hours and in from one to fourteen days most of these patients will go into labor and usually have an uneventful delivery. There is some increased risk of infection for both fetus and mother but our results for both are immeasurably better since we have discontinued the routine induction on all patients who had a spontaneous rupture of the membranes. We do not give sulfonamides and/or penicillin to these patients as a prophylaxis.

Cephalopelvic Disproportion.—We have not induced labor for many years where there was any evidence of disproportion either from a contracted pelvis or from an abnormally large baby. With cesarean section as safe as it is today the fetus should not have its life jeopardized or suffer permanent injury by induction of labor. We prefer that these patients go into labor and, if at the onset of labor there is marked disproportion, the patient must have a cesarean section. If, after a careful test of labor according to our criteria, there has been no increase in dilatation or descent of the presenting part, we perform a laparotrachelotomy.

Induction of labor for the treatment of borderline pelvic contraction has been almost given up in this country. However, a second symposium⁵ on this subject in England in 1936 revealed that 40 British obstetricians were now against induction and 18 were in favor. The advocates of induction conceded a fetal mortality of 12 per cent or more although all reports stated the fetal mortality following induction for disproportion ranged from 17 to 21 per cent.

Postmaturity.—There are no criteria by which postmaturity can be determined either before or after delivery. We believe that the cervix is the best index. We do not induce labor because patients are at term or because they are overdue. Those patients in whom there is evidence of disproportion because of the size of the baby are permitted to go into labor, kept "clean" and, if necessary, a cesarean section is performed after our test of labor.

We believe it to be meddlesome obstetrics to bring patients into the hospital, attempt medical induction, and if unsuccessful, permit the patient to go home. If this can be carried out then obviously there was no need for the induction in the first place.

not ripe and dilated 1 or more cm. As a rule, S.O.P.P. will not produce uterine contractions at any period of pregnancy unless there is some dilatation of the cervix.

In those cases where a bag is indicated, it is used. It may be a rectal, vaginal, extra or intraovular bag. In general, we prefer to insert a bag large enough so that when it is expelled, the baby's head can follow. We attach no traction to the bag until eight to twelve hours after its insertion. We also do not use S.O.P.P. until the bag has been in place for eight to twelve hours.

Eastman⁷ stated that in 85 per cent of their primiparas the head was engaged at term. This has not been our experience for many years. In about half of the primiparas, a segment of the head is through the inlet but we rarely find the head engaged even at the onset of labor. In the multipara, the head, as a rule, does not engage until the patient is well along in labor or even until after the membranes are ruptured. If the doctor is experienced, the floating head is no contraindication to rupture of the membranes providing it is done as outlined. The inexperienced doctor should not induce labor under any conditions. If uterine contractions, which need not be painful, do not begin within eight to twelve hours after rupture of the membranes, fractional doses of S.O.P.P. are given subcutaneously at 20-minute intervals.

The Drew Smythe⁸ catheter which is used to rupture the membrane at the level of the baby's neck, draining off as much fluid as possible but still leaving a possible bag of forewaters, has been used extensively in various British hospitals. Labor usually begins in twenty-four hours; it may be delayed as long as three days and occasionally, as long as seven days. Some cases have required a second puncture of the membrane. There have also been deaths from sepsis after this method. We have aspirated amniotic fluid and injected solutions into the amniotic cavity through the abdominal wall to alter intrauterine pressures without being able to start labor.

Rupture of the membranes is the simplest and most effective method of starting labor. If the cervix is ripe, the duration of labor is shorter than normal. If the patients are unselected, Keettel⁹ and coworkers report no increase in the average duration of labor although there is an increase in the number of prolonged parturitions.

Technique for Induction

Proper Indications and Management.—If labor is induced, there must be no sedation except nitrous oxide or ethylene until the uterine contractions are occurring every two to four minutes, lasting forty or more seconds, and cervical dilatation (vaginal examination) is increasing; when morphine and hyosine or other sedation may be started.

Conditions.—A vaginal examination to make certain that the cervix is "ripe," that the presenting part is normal, and that there is no occult prolapse of the cord. Strip the membranes.

I. Medical: Subcutaneous injection of S.O.P.P. (obstetric) or pitocin (for toxemic patients, if available).

0 - 0.03 ml. (m 55).

20 min. - 0.06 ml. (m 1) (1 international unit) if no or weak contractions.

40 min. - 0.12 ml. if no or weak contractions.

60 min. - 0.20 ml. (m III) if no or weak contractions and repeat if needed until total of 1 ml. has been injected.

The senior obstetrician during his training had the opportunity of making frequent vaginal examinations and urges that this method of teaching be used more extensively. Certainly it is the only method which enables one to appreciate the importance of a "ripe" cervix for the successful induction of labor.

The "ripe" cervix in the primipara is one in which there is complete effacement and the cervical margins are 0.5 to 1.0 cm. thick and soft. The dilatation varies from none to 3 cm. In the multipara the canal may or may not be effaced but in either case there are 2 or more cm. dilatation and the cervix is soft. Obviously, we disagree with the authors of the various textbooks who have accepted Stieve's report. The latter stated that at term the primiparous cervical canal is 3 cm. long and that there is no dilatation. Stieve's studies are based on sections obtained at autopsy and we believe his subjects were three or more weeks from delivery although they may have been at term by menstrual date. The senior author has been periodically measuring the vaginal portion of the cervix or of the canal, if there was sufficient dilatation, for over twenty years. Studies using x-ray technique for demonstrating the length of the cervix are in progress.

Table III lists the average duration of latent period and of labor for the various methods. No conclusions are permissible because several of the groups are too small but there seems to be some indication that labor after spontaneous rupture of the membranes is longer than after artificial rupture. This is what one would expect at least in our hands because we do not rupture membranes unless the cervix is ripe. As most recent statistics indicate, the average duration of labor in both primipara and multipara is definitely less than the usual figures given in textbooks, namely eighteen and twelve hours, respectively.

TABLE III. AVERAGE DURATION OF LATENT PERIOD AND OF LABOR: HOURS

| INDUCTION METHOD | PRIMIPARAS | | MULTIPARAS | |
|--------------------------------------|---------------|-------|---------------|-------|
| | LATENT PERIOD | LABOR | LATENT PERIOD | LABOR |
| S.O.P.P. and Pitsulfonate | 1.8 | 13.3 | 1.6 | 7.1 |
| S.O.P.P. and Pitsulfonate after R.M. | 1.7 | 11.7 | 1.5 | 9.0 |
| Rupture Membranes | 4.0 | 8.6 | 4.7 | 6.0 |
| R.M. and S.O.P.P. | (3.4) | (9.2) | 7.7 | 7.7 |

() = less than 10 cases.

R.M. = ruptured membranes.

Methods

We do not use bougie, bougie and pack, pack, stomach, or rectal tube or the intra- or extraovular injection of ether, uroselecton, hypertonic glucose or saline solution, etc. Castor oil or castor oil and quinine have also been discarded because they are of no value. If labor is to be induced with the most favorable outcome, a sterile vaginal examination must be made and the condition of the cervix determined. If it is ripe, one can be almost positive that the induction will be successful. At the time of the initial vaginal examination one must determine that there is not a forelying loop of cord or abnormal presenting part. If one contemplates a medical induction, the membranes should be stripped as high in the uterus as possible. The next morning the lower bowel is emptied by either a suppository or an enema and then either a medical induction with S.O.P.P. or rupture of the membranes is carried out. Our experience has been that induction with S.O.P.P. will fail if the cervix is

In the hemorrhagic groups the patients should be delivered vaginally if they possibly can be without undue hemorrhage.

In the toxemic patients one must evaluate the condition of the cervix and the severity of the toxemia. If the latter permits delay, the cervix will change and permit relatively safe induction of labor.

Induction of labor for postmaturity, contracted pelvis, convenience of patient or doctor is contraindicated.

Rupture of the membrane is the simplest and safest means of inducing labor.

Spontaneous rupture of the membranes does not necessarily imply that induction by some other means must follow.

The incidence of attempted induction of labor on our service is 3.2 per cent, and of failure is 9 per cent.

Castor oil or castor oil and quinine have no place in the induction of labor.

A vaginal examination using sterile technique should proceed all attempts at inducing labor. A careful evaluation of the pelvis, the determination of the presenting part and the exclusion of a concealed prolapse of the cord as well as the condition of the cervix must be determined. If the cervix is "ripe," labor can be successfully induced and delivery completed within twenty-four hours in over 80 per cent of the patients.

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Discussion

DR. IRVING F. STEIN.—In considering Dr. Grier's contribution, the question arises whether it is justifiable to perform induction of labor for convenience and expedience

II. Mechanical:

- a. If there is no palpable cord, strip the membranes and then rupture them, permitting as much fluid as possible to escape.
If no contractions develop within eight to twelve hours, proceed as in I. or attach 200 to 500 Gm. weight to bag or forceps.
- b. Bag: Vaginal, intra- or extraovular.
- c. Fetal Traction:
Head—Vulsellum or Willets forceps with weight.
Leg—Fillet and weight if fetus is dead. If fetus is alive, use an adhesive skin traction.

The use of estrogen or stilbestrol for three or more days prior to the induction has been useless in a small series. If the drug or procedure used is to be given therapeutic credit, the latent period cannot be too long because eventually labor will begin in all pregnant patients.

The minute and repeated injections of S.O.P.P. used for safety are unnecessary if pitsulfonate¹⁰ is available. The latter is a suspension of S.O.P.P. from which the active hormone is slowly liberated. The induction requires less time and there are fewer failures.

Rupture of the uterus, shock, anuria and death have been attributed to injections of S.O.P.P. One of us has seen rupture of the uterus in five patients (two died) with amounts of S.O.P.P. ranging from 0.2 to 0.3 ml.

Fatal anuria has been reported but reports by McQuarrie and co-workers¹¹ and our own studies indicate that even though repeated injections of S.O.P.P. are given, eventually a diuresis occurs.

S.O.P.P. produced a tetanic contraction of the uterus in five patients, 2.3 per cent. There were no uterine ruptures or fetal deaths or injuries. The uterine spasm begins to relax in five to ten minutes because of the stagnant anoxia and since it requires this long to anesthetize with chloroform and much longer with ether, it is obvious that the latter drug and probably the former also are useless for the treatment of this condition.

Pituitrin shock and/or sensitivity to pituitrin with death have been described in several reports.¹² Adelman and Lennon¹³ warn against its use but in their discussion speak of "when repeated injections of pituitrin are contemplated, conservative doses should be the rule, averaging 10 to 20 pressor units for the individual dose." These are tremendous doses to use at one injection in any patients and especially in obstetric.

One of us has had a long experience at two hospitals where S.O.P.P. was used in tens of thousands of patients in judicious doses and excluding the cases of rupture of the uterus, two of which certainly could have been prevented, he has seen no patient whose life was in jeopardy from the use of S.O.P.P. There is no drug or substance that is not toxic if given in abnormally large amounts—even water is toxic under certain conditions. There is no reason why S.O.P.P. should not be used by the experienced physician. During the past year, over 1,000 patients have had 1 or 2 units of S.O.P.P. injected intravenously during the end of the second stage with no reactions.

Summary

Termination of pregnancy by induction of labor after thirty-two weeks has less indication today than it had twenty years ago. It is inevitably followed by an increased maternal and fetal morbidity and mortality irrespective of how carefully the cases are selected.

The indications for induction of labor are selected cases of placenta previa, abruptio placenta, eclampsia and nonconvulsive toxemia of pregnancy.

Grier, the use of morphine in the first stage, the use of caudal anesthesia and other analgesics. I am sure that if you add them all up nothing much has happened over a period of years.

As near as I can tell in properly selected cases, there is no need to induce labor except for the convenience of the patient and the convenience of the physicians. I call your attention further to the fact that Dr. Grier quotes statistics on induction of labor. I am assuming that these inductions were done only in perfectly normal patients at or near term, not including the case of the infant that weighed five and three-fourths pounds. In these patients he has a much smaller morbidity than in the patient in whom labor is not induced; in fact, the gross fetal mortality was less than in patients who go into labor spontaneously. I am at a loss to know why stupid Nature over a period of a million years has not found that the mortality and morbidity of these patients will be decreased if she would have sense enough to rupture the membranes before the patient goes into labor.

DR. W. C. DANFORTH.—He who terminates a pregnancy before the normal onset of labor or who interferes operatively with the course of labor must be sure that he does not expose the patient to danger from which she would otherwise have been safe, and he must be certain that the procedure which he contemplates is indicated. Only in a minority of all cases of pregnancy will the initiation of labor artificially be necessary.

I agree that induction, because of cephalopelvic disproportion, should not be done, and that postmaturity alone does not warrant interference. I have on two occasions heard internists suggests that termination of labor should be done before term in cases of heart disease on the supposition that, as the baby is smaller, the labor will be easier. Any one with any real experience in obstetrics knows that this is a false hope and that induction done under such circumstances is likely to result in an unproductive labor, the woman experiencing pains perhaps for hours with no progress. An unnecessary burden is added to the already embarrassed circulation.

Dr. Dieckmann stated an important fact when he said that the cervix is the best guide. Induction, when the cervix is closed and uneffaced, is likely to require too much interference and the labor, in many cases, will be long and perhaps difficult.

I believe that packs, bougies, and the intrauterine use of chemical stimulants have no place in the obstetrics of today. Bags should be used only seldom. They may be useful in some cases of placenta previa in which delivery through the natural passage is elected and in an occasional case of toxemia in which haste is needed.

Except when termination of pregnancy is urgently indicated, induction should not be attempted when the cervix is uneffaced and closed. In cases in which such a cervix is found, and termination of pregnancy is urgently indicated, as, for example, in severe toxemia, especially in a primipara, the relative advantages of induction as compared with abdominal delivery should be carefully evaluated.

In all other cases induction should not be considered unless the conditions for easy starting of labor are present. By this is meant a cervix in which effacement is well advanced and in which some dilatation is found. The dilatation should be from one to three centimeters, and the nearer it is to the latter figure the better. In cases such as this, if the patient lives at a considerable distance from the hospital, the great haste needed to get the expectant mother to the hospital in time, and the embarrassment following a possible failure, may be avoided. Induction with these conditions present requires a minimum of trauma and morbidity is influenced but little. I agree with the statements of Dr. Dieckmann concerning the inductions formerly done which were followed by an increased fetal mortality and by maternal morbidity. I also went through a period during which we used bags in particular far more often than we do today and when we were not as selective as we are now concerning the state of the cervix. The change in our attitude toward induction has been a fortunate one.

I believe, also, that castor oil and quinine have had their day and are happily on their way to oblivion. We have found that the use of calcium, usually in the form of calcium gluconate, intravenously, followed by very small doses of pituitrin, is an effective

rather than for obstetric reasons. One must first be reconciled to accept as proper the termination of pregnancy for the reasons stated, and then consider the method employed and the results.

There is no doubt that it has advantages for both patient and doctor to plan labor by appointment, but the criteria of maturity and means of accomplishment must insure the safety of both mother and her newborn babe. Dr. Grier's analysis discloses that no harm resulted from induction of labor insofar as the mothers were concerned, but the neonatal death of a baby delivered two days past the estimated due date tends to question the criteria of maturity. This child weighed five and three-fourths pounds, atelectasis being found at autopsy, suggesting prematurity. It is well known that no method of estimating full maturity of the child is entirely dependable.

A poll taken of the members of the obstetric staff at Michael Reese Hospital revealed that, although we do not routine inductions, the one method most commonly used for induction of labor is the administration of castor oil, a method abandoned by the essayist. I feel that castor oil, though objectionable to some women, is readily accepted by most obstetric patients and is a highly effective drug if given at the proper time. When given after the patient shows signs of imminent labor, after a mucous discharge or spotting, and when the cervix is completely effaced, castor oil (two ounces) usually initiates labor, no other procedure being necessary. The term "partial effacement" as employed by Dr. Grier is indefinite and is capable of a wide variance in interpretation. It is my opinion that the initiation of labor by the use of castor oil is accomplished by the removal, via the intestinal tract, of some substance which has prevented the physiologic action of the posterior pituitary gland secretion. Following the removal of this inhibitory substance, the uterus responds to the normal (posterior) pituitary stimulation, labor usually following with strong contractions and of short duration.

Success of any method of induction is assured if the cervix is fully effaced and dilated two or more centimeters. If Dr. Grier had limited himself to these criteria, his latent period would be shorter as well as the duration of labor. In estimating the latent period, had Dr. Grier figured from the time of the enema, or from the administration of calcium gluconate, instead of time of rupture of membranes, his figures would have been increased by two or more hours. They are part of his routine induction procedure.

As to the method of puncturing the membranes, I cannot subscribe to puncture with a dressing forceps guided by rectal touch alone. This I believe to be a crude and wholly unwarranted method. A comparison made some years ago at Michael Reese Hospital revealed that a single vaginal examination early in labor or before the onset of labor carried no more danger of increased morbidity than did a rectal examination. Repeated vaginal examinations definitely do increase the risk of infection. By carrying a perforator, such as our "midwife's fingernail," in the examining finger, and using it only when conditions are favorable, one need not use blunt instruments or other devices requiring a second vaginal insertion. One group at Michael Reese Hospital who induce labor electively insists that it is requisite to drain off all or most of the liquor, taking ten to twenty minutes to do so, to insure prompt uterine response to rupture of the membranes. Dr. Grier apparently obtained a satisfactory result without so doing. I would like to have him discuss this point. Does Dr. Grier claim to be able to detect forelying cord by rectal examination? How accurate is the routine diagnosis of effacement and dilatation by rectal examination alone? One is often mistaken in the rectal diagnosis.

I believe there is some justification for elective induction in selected cases, and Dr. Grier has specified conditions under which it may be carried out. Whether his method of induction is superior to others commonly employed can be best evaluated by comparison of data and results.

DR. JAMES E. FITZGERALD.—Those of you who have sat on the Maternal Welfare Committee quite well know that many patients come to the hospital with rupture of the membranes but not in labor. I also call your attention to the fact that many methods have been devised in which labor has been shortened, which includes the method of Dr.

An analysis was made of neonatal deaths occurring in Chicago during the year 1944. Those included the cases where there was medical or mechanical induction of labor, and termination by cesarean section, where there was no labor. The general figures showing the number of births and deaths for the year 1944 are shown in Table I.

TABLE I

| | NUMBER | RATE |
|------------------------------|--------|------|
| Live births in Chicago | 59,430 | 20.1 |
| Infant deaths (under 1 year) | 1,789 | 30.1 |
| Stillbirths | 1,397 | 23.5 |
| Neonatal deaths | | |
| Under 30 days | 1,250 | 21.0 |
| Under 14 days | 1,173 | 19.7 |
| Maternal deaths | 93 | 1.6 |

There were reviewed 1,145 case reports of neonatal deaths. The majority of these deaths occurring in the first few days of life; in only one case included here was the period over fourteen days. This was a tentorial hemorrhage, and the patient lived twenty-nine days.

TABLE II

| | | |
|--|----|----|
| Number of cases in which labor was induced | | 26 |
| Medical | 12 | |
| Mechanical | | |
| Rupture of bag of waters | 13 | |
| Bag (all placenta previa) | 7 | |
| Other means | 3 | |
| Vaginal pack | | |
| Manual dilatation | | |
| Self | | |
| Termination by cesarean section | | 85 |
| Low cervical | 48 | |
| Classical | 33 | |
| Porro | 2 | |
| Vaginal—1, unknown—1 | 2 | |

TABLE III

| | | |
|--|---|----------|
| Indication for induction | | 26 cases |
| Placenta previa | 9 | |
| Toxemia (non-convulsive) | 6 | |
| Abruptio placentae | 1 | |
| Spontaneous rupture of bag of waters at term | 3 | |
| Postmaturity | 4 | |
| Uterine inertia | 1 | |
| Others: pyelitis, self | 2 | |

TABLE IV

| | | |
|----------------------------------|----|----------|
| Indications for cesarean section | | 85 cases |
| Placenta previa | 25 | |
| Toxemia (non-convulsive) | 21 | |
| (convulsive) | 3 | |
| Abruptio placentae | 10 | |
| Previous cesarean section | 14 | |
| Disproportion | 3 | |
| Previous dead babies | 3 | |
| Medical | 4 | |
| Poliomyelitis | 2 | |
| Tuberculosis | 1 | |
| Diabetes | 1 | |
| Carcinoma of cervix | 1 | |
| Acute hydramnios | 1 | |

method and one which avoids the frequent soiling of the sterile field which occurs with castor oil and also injury to the infant which possibly may follow the use of quinine.

I do not like the stripping of the membranes. We had a considerable experience with this before the relative harmlessness of rupture of the bag, under proper conditions, became apparent. High stripping in particular requires far more invasion of the cervix and lower segment than does simple rupture, with a consequent greater likelihood of subsequent infection.

Dr. Dieckmann states that rupture of the membranes is the most effective method for the starting of labor. Rupture of the membranes may be done with any convenient instrument. We have found, especially in cases in which dilatation is two to three centimeters, and in cases in which rupture may be indicated later in labor, that the long rod-shaped perforator of Hillis, which has a sharp point at the end, may be guided by the rectal finger and the membranes ruptured. A modified dressing forceps for the same purpose has been devised by Dr. De Costa of Michael Reese. This requires a minimum of vaginal manipulation and it is recommended to those who have not used it. The low morbidity following a considerable series of inductions in our service, which has been reported this evening by Dr. Grier, I am sure, is due to the reduction of manipulation to the absolute minimum.

Induction should not be done without accurate knowledge of the pelvis and the certainty that disproportion is not present. An occult fore-lying cord should be carefully excluded. I agree fully with the statement of Dr. Dieckmann that when the cervix is "ripe" induction is nearly always successful. Induction through an undilated and uneffaced cervix may be a formidable procedure.

DR. HERBERT E. SCHMITZ.—On our service at Mercy Hospital-Loyola University Clinics we are using induction of labor where there is definite indication for the termination of pregnancy. We have considered for some time that induction for convenience is meddlesome obstetrics, although it is being carried on by one or two members of the staff but no longer with the sanction of the Department. Our opinion was based on a study carried on in 1933 to 1935 in which 200 cases were induced electively so we might evaluate the procedure. Our procedure is to send the patient to the hospital in the late afternoon, give castor oil in the morning followed by a high cleansing enema. The patient is then draped and a sterile vaginal examination is performed. We are of the opinion that only by means of a vaginal examination can we determine whether or not you have a so-called ripe cervix. No matter how much experience you have had and no matter how efficient you are in rectal examination, there is always a difference in the findings on the vaginal examination. If it is found that the cervix is ripe and there is complete effacement and at least a degree of dilatation, the membranes are then stripped as high as we can reach and then perforation of the amniotic sac is carried out. The fluid is drained as completely as possible by ballotting the head with the finger. The patient is returned to bed and if labor does not start in two hours, pituitrin is used intramuscularly in one minim doses. In this group of patients we had the same experience as to the rapidity of labor in relationship to the latent period. This I believe demonstrates conclusively our inability to recognize which cervix is ripe. The more rapid labor must mean that this procedure induces stronger contractions of the uterus, otherwise how could we account for the more rapid labor?

Feeling that this was true, I made a careful study of the postpartum period of these patients and I was surprised at the increased damage to the soft parts.

As far as commenting on Dr. Dieckmann's observation regarding priming of the cervix with estrogens before induction of labor, we have had considerable experience with this method and feel it is of no value.

DR. LUELLA E. NADELHOFFER.—Dr. Dieckmann thought it would be interesting to approach this subject from another direction, that is, from the standpoint of neonatal deaths.

In closing, there is a great deal of material for study of obstetrical practice in a review of neonatal deaths. It would also be worth while to review the cases of stillbirth occurring during labor and delivery and obstetric procedures where the mother and baby "got by."

DR. J. P. GREENHILL.—If Dr. Dieckmann is correct, that in the De Lee-Greenhill book I left in Stieve's illustration of the long cervix at term, I want to apologize. However, I am certain I did not leave it in because I do not agree with Stieve. In at least two places in the book is an entire paragraph emphasizing that regardless of a woman's calculation of the date of the last menses, if the cervix is not partly effaced and dilated the patient is not at term.

Tonight we dealt with two entirely different problems. (1) Elective induction, and (2) induction for medical and obstetric indications. Dr. Nadelhoffer's figures are not pertinent because they represent what Dr. De Lee used to call "rotten obstetrics." The two papers we heard, emanated from excellent obstetric institutions. The subject under discussion is for specialists only and not for general practitioners. I do believe that at times elective induction of labor is advisable. Every one employs a different procedure for this purpose. I strip the membranes, rupture the membranes and order an enema one hour afterwards. I rarely use pituitary extract. I never employ a bag, bougie or gauze pack. In experienced hands there are practically no dangers. The conditions which must be fulfilled are, no disproportion, a partly effaced and dilated cervix, a head presentation (although Grier reported several cases of breech presentations), and engagement of the head.

We must differentiate between elective induction in normal women and induction of labor in sick women. A certain proportion of the latter will have trouble after induction of labor.

DR. DIECKMANN (Closing).—Dr. Schmitz may be right about increased damage to the soft parts by inducing labor before the parts have been fully prepared. We have studies in progress now to determine that, but it is extremely difficult to determine the results of labor in some quantitative manner.

I disagree with Dr. Greenhill. I believe Dr. Nadelhoffer's figures are pertinent. These maternal and fetal deaths occurred during the past two years in the city of Chicago. As long as specialists try these various methods for terminating pregnancy, less experienced doctors are also going to try them with inevitable damage if not fatality. Many of the fetal and maternal deaths which occur are preventable.

I have seen quite a few expert obstetricians carry out routine induction of labor. Almost without exception each specialist has sooner or later a fetal or maternal fatality due to the induction. Having learned this during my residency, I have been extremely cautious in inducing labor in a normal patient for either the patient's convenience or mine. To date I have had no fetal or maternal mortality but I believe that there is an inevitable mortality associated with such procedures. I have had labor induced in toxemic patients and have had both fetal and maternal mortality. It has always been due to the fact that there were too many "cooks."

The number of cases induced by medical or mechanical induction and the number terminated by cesarean section, and the types of each procedure, are shown in Table II.

In seven cases of medical or mechanical induction, a combination of two or more methods was used. In one of these, in a patient with vaginal bleeding, 1 c.c. of pituitrin was given, the bag of waters was ruptured, vaginal packing and manual dilatation were all tried.

In eight of the 12 cases of medical induction, pituitrin was used; in three cases, intranasally. One case was self-induced.

The indications for medical or mechanical induction are shown in Table III.

The indications for termination by cesarean section are shown in Table IV.

The cause of death most frequently given in the 111 cases was:

| | |
|--------------------------------|----|
| Prematurity and/or atelectasis | 67 |
| Congenital malformations | 14 |
| Intracranial hemorrhage | 8 |
| Bronchopneumonia | 7 |
| Erythroblastosis | 5 |
| Cause unknown | 13 |

The weight of the babies was:

| | |
|-----------------|----|
| Under 2,500 Gm. | 83 |
| Over 2,500 Gm. | 24 |
| Unknown | 7 |

Loss of fetal life is to be expected in a high percentage of cases where the indication for interference is hemorrhage or toxemia. One would expect where the indication for cesarean section is disproportion or repeat section, to have a living baby.

Disproportion, 3 cases:

1. 2,200 Gm.—umbilical hernia.
2. 3,634 Gm.—anencephalus and spina bifida diagnosed before operation.
3. 4,325 Gm.—hydrocephalus and spina bifida, diagnosed by x-ray before operation.

Repeat cesarean section:

- 3 had congenital malformations.
- 1 an associated placenta previa.
- 1 an associated toxemia.
- 10 weight of babies 1,360 to 2,900 Gm., atelectasis.

There were two maternal deaths:

1. A 30-year-old gravida iii, 34 weeks gestation. Toxemia, blood pressure 205/130. Classical cesarean section. Died of vaginal hemorrhage ten hours postoperatively.
2. A 37-year-old, gravida i, 28 weeks gestation. Toxemia with three convulsions. Classical cesarean section. Died from shock two hours postoperative.

The 93 cases of maternal death occurring in 1944 were also reviewed. In five cases labor was induced by mechanical means.

1. Convulsions in a 15-year-old gravida i; ruptured bag of waters.
2. Toxemia in a 275 pound patient with hypertension and 4+ albumin; 35 weeks gestation. Bag reinserted once. Died undelivered.
3. Toxemia with convulsions, 33 weeks gestation. Died undelivered.
4. Toxemia, 32 weeks gestation. Manual dilatation. Sepsis.
5. Bleeding, 33 weeks gestation. Manual dilatation. Hemorrhage.

It may be commented that, while in the majority of these cases, neonatal death was to be expected, contraindicated procedures were used in some cases and poor judgment was shown in choosing cesarean section in some cases (monstrosity) and in the time repeat section was performed in others.

4. The cervix should be soft, partially effaced, and dilated to at least one centimeter. These are the signs which usually precede the onset of normal labor.

In short, the onset of labor should be imminent, and obstetric prognosis good, for the elective induction of labor.

Method of Induction

When the above conditions are found upon rectal examination, the patient is informed that she may go into labor at any time. She is told that if she so desires she may select a time in the near future for her delivery. This can be made at a time most convenient for herself, her family, and her husband, to say nothing of the physician. She can make arrangements for the care of her household. In these days this is an important consideration. If she has had precipitate labors in the past, a repetition of this experience can usually be avoided by inducing labor. The patient usually enters the hospital in the morning after a night's sleep at home in her own bed. She has been instructed to have no breakfast, as anesthesia is far safer when the stomach is empty. She is admitted in a happy frame of mind without confusion. The nurse, anticipating her arrival, takes her in charge without hurry, then gives her a careful perineal preparation and a hot soapsuds enema. Soon after this the intern gives her intravenously, 10 c.c. of 10 per cent calcium gluconate solution. Usually within two hours the physician ruptures the membranes artificially. In some instances this is not necessary, as labor is so near that spontaneous rupture will follow the enema. Before the bag of waters is ruptured the perineum and vulva are cleansed with soap and water and an aqueous solution 1:2,000 zephiran chloride is poured freely over the introitus. The rupture may be done with a sterile gloved finger in the vagina to guide a perforator through the cervical opening to the membrane. We often prefer to use a dressing forceps guided rectally. We believe this does not cause as much trauma and introduces fewer bacteria than rupture done vaginally. The use of a sharp pointed perforator is more likely to leave scratches on the infant's scalp, and possibly laceration in the vagina or cervix. Before rupture is attempted the obstetrician should be certain that a foreshortened cord is not present. If the presenting part is fitting well into the lower uterine segment, prolapse of the cord is almost impossible. The fetal heart tones should be observed before and frequently after artificial rupture.

If labor ensues within two hours, it is allowed to progress without further stimulation. If it does not, one minim doses of pitocin are given into muscle and repeated at thirty- to sixty-minute intervals. Usually no more than two doses are required. In this series, 36 women went into labor without any need for pitocin. In none was any evidence of tetanic contractions observed.

Results

In the year from Aug. 1, 1945, through July 31, 1946, 1,284 women were delivered. There were 129 inductions, an incidence of 10 per cent. Only six of these were induced for therapeutic reasons. Four were because of severe toxemia, and two for marginal placenta previa. All the rest were considered elective inductions. There was only one which could be considered a failure. This patient was a multipara. It was thought by the physician that her membranes were ruptured artificially but they were not. This case was improperly chosen in that the head was entirely too high. She did go into labor and dilated to 7 centimeters. An x-ray revealed the infant was presenting by the face with the chin posterior. After eight and one-half hours of labor she was delivered by low cervical cesarean section.

ELECTIVE INDUCTION OF LABOR*

R. M. GRIER, B.S., M.D., EVANSTON, ILL.

(From the Evanston Hospital)

FROM Nov. 1, 1935, through Oct. 31, 1945, 10,439 women were delivered at the Evanston Hospital. Excluding bag inductions, 1,353, or 12.9 per cent, had their labors induced. In the first five of these years the incidence of induction was 10.9 per cent, and in the latter five years, 14.4 per cent. Because of this trend in our hospital, and because this procedure has been considered, by some, to be meddlesome obstetrics, it was believed that a study of our results should be made. It was our impression that our results, for both mother and child, had been good. This study has therefore been made to substantiate or disprove this impression. For one year, starting Aug. 1, 1945, a chart was kept in the labor room for recording of results when the data were fresh in the minds of all concerned. The house staff who kept these records was enthusiastic and gave constant attention to details. We therefore believe the estimate of the onset of labor may be considered accurate.

During the ten years before this study, we had made several changes in our technique for the induction of labor. We discontinued the use of castor oil, the value of which was doubtful and which was extremely unpleasant to the patient. Since the war quinine has not been available. Its absence has been beneficial, for too frequently it produced only annoying contractions, which were occasionally tetanic in character. The demonstration of deafness in the newborn following the use of quinine should outlaw this drug in obstetrics.¹ The so-called loosening or stripping of the membranes, also of dubious value, has been discontinued. In at least one case in our hands some years ago, this procedure was followed by a severe intrapartum infection which began three days after failure to start labor. We discontinued the use of obstetric pituitrin in doses as large as three minims, and now rarely use more than one minim doses. In none of the cases here reported have we observed tetanic contractions.

In the past five years a much simpler and more efficient method has developed.

Selection of Cases

We believe certain conditions should be present before the induction of labor is attempted, especially when there is no therapeutic indication. We would like to re-emphasize these important conditions, which, I am sure, are well known to all obstetricians of experience.

1. There should be no cephalopelvic disproportion.
2. The baby should be mature and should preferably present by the vertex.
3. The fetal head should be engaged or dipping well into the pelvis. It must not be floating or ballotable.

*Read before the Chicago Gynecological Society, Nov. 15, 1946.

TABLE III. AVERAGE LENGTH OF LABOR IN MULTIPARAS

| 4 hours 8 minutes \pm 12 minutes | |
|------------------------------------|----|
| Total 95 | |
| More than average | 32 |
| Less than 8 hours | 26 |
| Less than 12 hours | 3 |
| Between 16 and 20 hours | 3 |

It is our contention that the more completely the conditions described above are fulfilled the more smoothly will induction and labor proceed. We have compared the latent time and duration of labor in those women who have findings adequate for the induction of labor, such as slight effacement and only one centimeter dilatation of the cervix with those in whom these conditions were more advanced, namely moderate effacement to complete effacement and more than one centimeter dilatation of the cervix. There were 67 women in the former group. The time from the rupture of the membranes to the onset of labor was 1 hour 18 minutes \pm 11 minutes. However in the latter group, there were 62 in whom the latent time was only 44 minutes \pm 6 minutes. The duration of labor in the former group was 6 hours 18 minutes \pm 39 minutes. In the latter it was 3 hours 33 minutes \pm 14 minutes. Apparently the short time for the latent period and the short duration of labor verifies our contention. These results are shown in Table IV.

TABLE IV. LATENT PERIODS AND DURATION OF LABOR

| | NO. CASES | RUPTURED B.O.W. TO ONSET LABOR | DURATION OF LABOR |
|--|--------------|-----------------------------------|-----------------------------|
| Slight effacement and only 1 cm. dilatation | 67 | 1 hr. 18 min. \pm 11 min. | 6 hr. 18 min. \pm 39 min. |
| Moderate to complete effacement and over 1 cm. dilatation | 62 | 44 min. \pm 6 min. | 3 hr. 33 min. \pm 14 min. |

The same may be said for another important condition, the station of the fetal head. Here two groups are shown in Table V.

TABLE V

| | NO. | | |
|---------------------|-----|-----------------------------|-----------------------------|
| Station—1 to -3 cm. | 78 | 1 hr. 36 min. \pm 14 min. | 5 hr. 30 min. \pm 24 min. |
| Station—1 or lower | 51 | 29 min. \pm 4 min. | 3 hr. 34 min. \pm 14 min. |

In the first group are placed those in whom the station was from one centimeter above the ischial spines to three centimeters above the spines, and the second included those in whom the station was lower than one centimeter above the spines. In the former group there were 78 women in whom the latent period was 1 hour 36 minutes \pm 14 minutes. In the 51 in the second group, the latent time was only 29 minutes. The duration of labor was also definitely shorter. In the first group it was 5 hours 30 minutes \pm 4 minutes and in the second, 3 hours 34 minutes \pm 14 minutes.

Most of these patients were given analgesia in labor. In the great majority demerol and scopolamine were administered and a much smaller number received nembutal and scopolamine. Practically all were given inhalation anesthesia by means of gas and oxygen for the termination of labor.

It was considered at the beginning of this study that an occiput posterior position of the fetal head would delay the induction time and prolong labor.

Only five women in this series became morbid as measured by a temperature rise as high as 100.4° F. This is less than our incidence for all deliveries which is usually between 5 per cent and 6 per cent. Only one of these was febrile for four days.

There was one stillborn macerated fetus and one neonatal death. The latter was a baby two days overdue, weighing 2,620 Gm., delivered spontaneously after a labor of two hours and eighteen minutes. Autopsy disclosed only fetal atelectasis. There were two breech deliveries, several manual rotations of the head when the occiput was posterior, and our usual incidence of low forceps and spontaneous deliveries.

Thirteen women were induced eight or more days before the estimated date of term. All of these were multiparas, and all the infants survived. Thirty-five were delivered within less than a week before term. The remainder were at term or beyond.

As a rule the labors were considerably shorter than has been the rule in our service. Table I shows the time from the rupture of the membranes to the onset of labor and the duration of labor for primiparas and multiparas.

TABLE I

| | [RUPTURED M.O.W. TO ONSET LABOR] | DURATION OF LABOR |
|---------------|------------------------------------|-----------------------------|
| Primiparas 34 | 2 hr. \pm 29 min. | 6 hr. 56 min. \pm 44 min. |
| Multiparas 95 | 55 min. \pm 5 min. | 4 hr. 8 min. \pm 12 min. |

The most important single thing in this method of induction of labor is the rupture of the membranes. This is the time at which induction begins. The latent period is considered as the time between this rupture and the onset of labor, that is, when contractions begin. A long latent period would tend to increase intrapartum and postpartum infections. Table I shows that the average latent period for primiparas is 4 hours \pm 29 minutes, and for multiparas 55 minutes \pm 5 minutes. The longest latent periods for primiparas were 22 hours and 15 minutes in one, and 8 hours in another. The longest latent period for a multipara was 6 hours and 30 minutes. Even these few relatively long periods are not actually as long as one might expect. Table I also shows that the labors are as a rule much shorter than what we have come to regard as usual. In primiparas the average length of labor was 6 hours and 56 minutes \pm 44 minutes, and in the multiparas it was 4 hours and 8 minutes \pm 12 minutes.

Of the 34 primiparas there were thirteen whose labors were longer than the average. These are shown in Table II.

TABLE II. AVERAGE LENGTH OF LABOR IN PRIMIPARAS

| 6 hours 56 minutes \pm 44 minutes Total 34 | |
|---|----|
| More than average | 13 |
| Less than 10 hours | 7 |
| From 10 to 14 hours | 3 |
| From 14 to 24 hours | 2 |
| 25 hours—10 minutes | 1 |

Of the 95 multiparas 32 had labors longer than the average. These are shown in Table III.

Thus it is seen from Tables II and III that extremely long labors were encountered in none and relatively long labors in a very much smaller number than is usually observed.

attention had been given to this subject, probably more women could have been selected for induction. However, it is not our ambition to induce labor in as many as possible.

Conclusions

1. The precipitation of imminent labor, by rupture of the membranes, can be very successful.
2. The proper selection of cases is most important.
3. The criteria for the proper selection of patients for induction of labor have been indicated.
4. Rupture of the membranes without the introduction of the hand into the vagina minimizes the introduction of bacteria.
5. The use of a dressing forceps, rather than a sharp pointed perforator, and its guidance through the vagina with a gloved finger in the rectum, is feasible and reduces trauma.
6. The use of quinine and castor oil is potentially harmful, often inefficient, and certainly unpleasant.
7. Calcium gluconate given intravenously has seemed to be a definite aid in producing normal and efficient uterine contractions.
8. Pituitrin in more than one minim doses is not necessary.
9. The maternal morbidity in this series is less than our general average for the past ten years.
10. The gross fetal mortality was less than 2 per cent, which is less than our general fetal mortality for these years.
11. A physician is justified in making labor easier for his patient, providing he can accomplish it safely.
12. The results here presented show that the elective induction of labor, in properly selected cases, or in other words, the precipitation of imminent labor, is a justifiable procedure.

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(For discussion, see page 504)

but this did not occur. There were posterior positions in 10 of the 34 primiparas and only half of these took longer than the average. Of the 95 multiparas, 31 had posterior positions and only 8 of these were longer than the average.

Discussion

Elective induction of labor has long been a subject of much controversy. Some regard it as meddlesome and vicious;⁴ others state that the membranes may be ruptured with impunity.³ We believe the procedure may be very successful in properly selected cases. We have tried in this report to show the most important conditions necessary for the selection of cases. I think we have all had failures with inductions and have been influenced by empirical laws laid down by our forebears who have condemned the procedure, rather than by a study which might show why some have failed and others have succeeded. We all have often seen long latent periods after spontaneous rupture of the membranes, when the cervix is undilated and uneffaced. In these women hours elapse before effacement takes place and dilatation begins. On the other hand, we frequently see women whose membranes rupture spontaneously, who go into labor immediately, and who sometimes deliver before they arrive at the hospital. This latter group of patients might have been spared this unfortunate experience if they had been examined more frequently rectally in the last month of pregnancy.

There are two points in which this procedure differs from other methods. Though minor, both are considered as of some importance. The first is the rupture of the membranes without introducing any part of the hand into the vagina.

The second is the use of calcium rather than castor oil and, or, quinine. Calcium has been shown clinically and experimentally, to be an effective stimulant to uterine contractility.² It has been suggested that an increase in the ionized calcium is requisite for the spontaneous onset of labor at term. Though the dose which is employed here is small and the effect on total circulating calcium is transient, it is believed that its administration may so alter the ratio of ionized to nonionized calcium as to increase uterine contractility. We have the distinct clinical impression that it is useful, and it is offered, therefore, as part of the method for the induction of labor here presented. The use of castor oil is not only disturbing to the patient, but it is of questionable value. The demonstration of congenital deafness following the use of quinine should eliminate this drug from obstetric use.

From this study it does not appear to us that the increase in the number of inductions at the Evanston Hospital during the past five years is cause for concern. Whereas the incidence for ten years has been 12.9 per cent, the past year in which this study was made, the incidence was 10.0 per cent. Only one induction in this series could be considered a failure. No such detailed study of this procedure has been made for the previous ten years, but it had been our impression that the results did not forbid its continued use. If still more

TABLE I

| | SINGLE COM- PLAINT | TWO COM- PLAINTS | THREE COM- PLAINTS | FOUR COM- PLAINTS | TOTAL CASES | PER CENT |
|------------------------|--------------------------|------------------------|--------------------------|-------------------------|----------------|-------------|
| Abdominal pain | 79 | 28 | 7 | 1 | 115 | 36 |
| Menstrual disturbances | 55 | 15 | 1 | 1 | 72 | 23 |
| Venereal disease? | 49 | 1 | | | 50 | 16 |
| Vaginal discharge | 15 | 22 | 4 | | 41 | 13 |
| Urinary complaint | 5 | 4 | 12 | 2 | 23 | 7 |
| Miscellaneous | 16 | | | | 16 | 5 |
| | 219 | 70 | 24 | 4 | 317 | 100 |

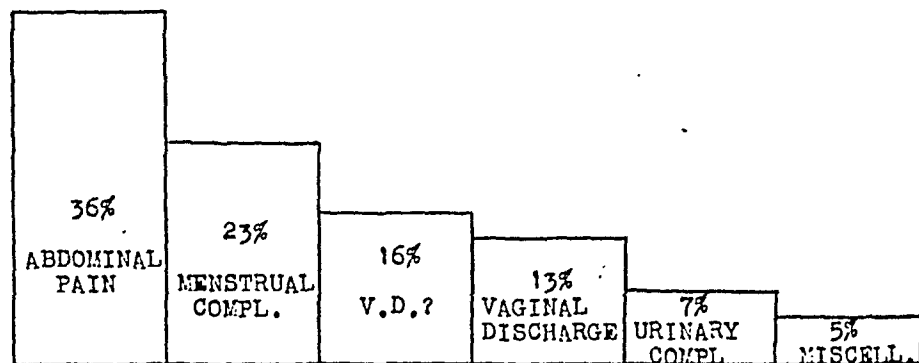


Fig. 1.—Chief complaint in 317 cases of gonorrhea in women.

Analysis of Symptoms

1. Over one-third of the women (36 per cent) found to be infected with gonorrhea came into the clinic because of abdominal pain. Of the 115 cases who presented themselves with this complaint, 79 women had abdominal pain only, while 36 had one or more complaints accompanying abdominal pain (Table I). The pain was of varying duration and location. Thirty-eight women (33 per cent) said their pain had lasted one to three days before they came to the doctor. Twenty-one (18 per cent) had had pain four to seven days before they sought help. In 28 cases (24 per cent) the pain had lasted one to four weeks. Sixteen women (14 per cent) had had pain for one month or longer before they entered the clinic. Twelve patients (11 per cent) did not know how long the pain had been present.

2. The second most frequent complaint presented was that of some menstrual irregularity. Seventy-two women entered the clinic because something had gone wrong with their menstrual period, the flow had become prolonged, menstruation had become significantly heavier than normal, or too frequent menstruation was complained about. These women did not suspect the nature of their disease, but frequently blamed the type of work they were doing for their difficulties. Stories like—"work in the shipyards does not agree with me," "sitting on cold steel makes me flow too much," often prefaced the stories of their complaint. The most frequent complaint in this group was prolonged flow. A typical story that we heard again and again was the one in which the woman stated that she had had a menstrual period of normal duration two weeks or only a few days before a new one started. This last period proved to be prolonged and unusually heavy. It was this abnormal period which usually brought the patient to seek medical help. This is such a characteristic story that we learned to put gonorrhea as our first differential diagnosis after hearing such a history. Two-thirds of the women with menstrual complaints showed the symptoms to be present for less than one month

GONORRHEA IN GYNECOLOGY*

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GONORRHEA is still the most prevalent communicable disease in this country. Health department statistics show the incidence of the disease on the increase. In January, 1946, there were 31,305 cases of gonorrhea reported in the United States as compared with an average monthly 25,229 cases for the year 1945.¹ Interviews with outpatient gynecology clinics reveal that in most clinics "gonorrhea is not a problem." We found that few cases of gonorrhea (in the early stages before they reach the operating table for salpingo-oöphorectomy) are found in the gynecologic practice of private physicians, yet the late complications are commonly seen in the operating room. However, if smears and cultures are taken routinely the picture changes considerably. Cooke and Lankford² reported an incidence of 22.8 per cent of positive cultures in women attending the outpatient department of obstetrics and gynecology in Galveston, Texas. The discrepancy between the case finding of gonorrhea in male and female is great. The obvious symptoms in the male bring the patient to the physician. But why does the infected female so frequently escape the attention of the gynecologist until the patient becomes a surgical problem?

During the year March 1, 1944, to Feb. 28, 1945, 2,832 new patients were seen in the gynecologic clinic of Permanente Field Hospital, Richmond, California. This clinic served women who were employed in the Kaiser shipyards of the Richmond area, in which as many as 23,000 women were employed at one time. This clinic was not specifically known as a venereal disease clinic. Among the women seeking advice for one gynecologic complaint or another during that year 390 cases of gonorrhea were found. This means that 13.8 per cent of all new gynecologic cases were infected with gonorrhea (only bacteriologically proved cases were included in this series). This seems to be an alarmingly high percentage of venereal disease among patients in a gynecology clinic. We therefore became interested in analyzing the complaints with which these women presented themselves in order to learn what their reasons were for seeking medical help. We wanted to know whether they themselves suspected to be infected with a venereal disease and therefore came to the doctor, whether their symptoms were easily recognizable as those indicating gonorrhea, or whether their complaints seemed to be unrelated to gonorrhea. Three hundred seventeen of the 390 cases were analyzed. Table I demonstrates what we found.

*This work was carried out at the Department of Obstetrics and Gynecology, Permanente Foundation Hospitals, Oakland and Richmond, California.

6. Sixteen women (5 per cent) had various complaints. Some were wondering whether they might be pregnant (nine cases). Three patients thought they had had a miscarriage. This fear was prompted by unusually heavy bleeding with clots and cramps. Three women complained about nausea, one of backache.

Discussion

The analysis of the complaints shows that a large percentage of cases presented symptoms which are not usually mentioned or suspected of being characteristic of gonorrhea. Almost one-fourth of the patients presented themselves with menstrual difficulties, which could have easily led to the wrong diagnosis if bacteriologic studies had not been made. In view of the fact that irregular bleeding, prolonged bleeding which at times takes on the form of hemorrhages is often the only indication of the infectious process, we must consider the possibility that some pathologic changes occur in the endometrium. Especially important seems the fact that the irregular and heavy bleeding may already appear early in the disease. If the disturbed bleeding occurs early in the ascending process it may occur in the absence of involvement of the adnexa.

A review of the literature shows that there is no unanimity of opinion as to whether the endometrium is involved in the ascending gonorrhea. Nor does the American literature mention menstrual disturbances as a frequent symptom in women with early gonorrhea, whereas the European literature stresses this symptom commonly.

Barringer,⁴ discussing the symptoms of gonorrhea in the female, states "acute gonorrhea gives rise to few symptoms. There may be a little burning on urination, a slight discharge, a few colicky pains. But woman is so used to many of these symptoms. The discomfort, pain, and bladder symptoms she may consider part of a menstrual cycle." Discussing gonorrheal endometritis, Barringer says, "This condition giving rise to symptoms of menorrhagia and metrorrhagia is rare, but may be quite trying from a standpoint of diagnosis. These symptoms occur usually in young, poorly-nourished girls who have a primary virulent attack of gonorrhea. The bleeding occurs during the weeks of most active infection, and often is of such persistent type that one fears that an early malignancy may be overlooked. Presumably the bleeding is due to an acute gonorrheal endometritis with erosion which give rise to areas which bleed easily. The further probability of the uterus being in a posterior position and therefore heavy and boggy from infection adds to the mechanical element of passive congestion." Hitchman and Adler, as quoted by Te Linde,⁵ insist that inflammation of the endometrium never gives rise to bleeding from the uterus. Te Linde⁵ states that one frequently encounters irregularity in menstruation in acute gonorrhea, but is doubtful whether this is due to the presence of endometritis or to abnormal ovarian function dependent upon the presence of infection in the adnexa. Pelouze⁶ mentions the most common early symptoms as those of the urinary tract. He states that a study of the available data upon gonococcal endometritis shows a haziness regarding the condition. He quotes Eden and Lockeyer saying

(Table II), which only emphasizes the fact that the first abnormal period is so significantly altered that it brought the patient to the clinic.

TABLE II. MENSTRUAL DISTURBANCES

| LENGTH OF TIME PRESENT | NUMBER OF CASES | PER CENT |
|------------------------|-----------------|----------|
| Less than one month | 48 | 67 |
| One to three months | 5 | 7 |
| Four to six months | 4 | 6 |
| More than six months | 1 | 1 |
| Unknown | 14 | 19 |
| Total | 72 | 100 |

But there are other menstrual disturbances that might be brought on by gonorrhea. The prolonged flow that brings the woman into the clinic after having bled for three weeks or longer might prove to be caused by the gonococcus. The menses might remain prolonged and increased in amount for weeks, even months, or might recur every eight to fourteen days. Smears and cultures taken in these cases will often reveal the real cause of their difficulties. It is commonly believed that smears and cultures taken from a bleeding cervix are of little or no value. It has been our experience that bacteriologic examination at this time will solve many problems of "functional menorrhagia," if the technique is used correctly. The technique for the collection of the bacteriologic material has been expertly described by Pelouze.³ Material from the Skenes and Bartholins glands was collected in the usual manner. The cervix was exposed with a bivalve vaginal speculum. The cervix was then cleaned thoroughly with dry cotton applicators, and all blood and mucus wiped off. This cleaning of the cervix cannot be too much emphasized. Upon this procedure depends the success of the bacteriologist in making an accurate diagnosis. If the cervix is insufficiently cleansed the smear will be utterly confused by a multitude of organisms which may make the reading of the slide impossible, and the culture will be hopelessly overgrown by organisms. After cleaning, the cervix was then squeezed with the speculum blades to milk the cervical glands. A cotton applicator was introduced about 1 cm. into the cervical canal, and the material thus obtained spread thinly on a glass slide. Again the speculum blades were pressed together to obtain more material in the same manner for a culture. Even in a fast bleeding cervix this procedure proved to be satisfactory.

3. Fifty women (16 per cent) who proved to have gonorrhea came into the clinic wanting to know whether they had a venereal disease. They had had a suspicious contact or they just wanted a venereal disease checkup.

4. Forty-one women (13 per cent) complained about a vaginal discharge of varying duration and intensity. Some complained of and proved to have the typical creamy yellow discharge described in the textbooks as the characteristic symptom of gonorrhea. Others, however, presented as their chief complaint an itching, foamy, irritating green discharge, which is commonly seen in trichomonas vaginalis infections. Fifteen women registered vaginal discharge as their only complaint (Table I). Twenty-two women had one other symptom coupled with vaginal discharge. Abdominal pain was reported eight times in connection with the discharge. Burning, frequency, or dysuria was each coupled once with a discharge. The classical triad of vaginal discharge, frequency and burning on urination, was only reported in one case. It is worthy of note that only the fourth most frequent symptom was that of a discharge.

5. Twenty-three women (7 per cent) complained about some urinary disturbances. Frequency of urination and urgency, burning on urination, as well as bloody urine were among the complaints mentioned.

Conclusions

Menstrual disturbances in gonorrhea are a frequent finding. In our series it took precedence over the most widely quoted triad of symptoms of urinary frequency, urgency and vaginal discharge. In our experience it is important to make bacteriological studies on women even in the presence of bleeding. The so often quoted "higher level of suspicion" must be applied to patients in gynecological practice in order to prevent the tragedies of chronic gonorrhea which are only too familiarly seen on the operating table.

We wish to express our thanks to Martha Eaton, A.B., medical statistician, for her help in assembling the statistical material.

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"we do not as a rule meet with acute uterine gonorrhea in gynecological practice."

If we turn to the textbooks of gynecology, the information is rather scant indeed. Symptoms of acute gonorrhea are discussed very briefly. The most frequent symptoms mentioned are those of the urinary tract and vaginal discharge. Most textbooks give long and complete discussion to chronic gonorrhea but fail to impress the reader with the variability of symptoms in acute gonorrhea and only a rare sentence is devoted to the menstrual disturbance that so frequently is found in the early stages of the disease.

Franz,⁷ on the other hand, describing the symptoms of acute gonorrhea, states, "characteristic for the ascending corpus gonorrhea is the increased menstruation. This is partly caused by the inflammatory hyperemia in the mucosa of the uterus and partly by mucosal defects, which are caused by inflammation. The menstruation shortly after the infection is often like a hemorrhage, at times it remains prolonged and increased in amount for months." Discussing endometritis gonorrheica "in the acute stages there is inflammatory hyperemia, swelling of the mucosa, and an increase in secretion. In the chronic stage the inflammation is mainly found in patchy distribution. Gonorrhea of the uterus is an ascending infection. First the gonococci are distributed all over the epithelium, then they penetrate the interepithelial spaces into the superficial stroma spaces. Whether the gonococci penetrate into the depth of the glands or into the muscularis is still an undecided question." Wagner,⁸ in Halban and Seitz, mentions menstrual disturbances as frequent in gonorrhea. In 30 per cent of his cases the patient came to the physician only because of menstrual disturbances. He points out that the ascending gonorrheal process often follows a menstruation. This period in many cases may already be prolonged and more profuse than the previous ones. Or after a pause of only a few days profuse bleeding starts, which at times persists for several weeks with only short interruptions. Menstruation occurs too often, is prolonged and profuse. Thaler⁹ found menstrual disturbances in 30 per cent of his patients with gonorrhea, Goth¹⁰ in 31 per cent of his 700 cases. Wertheim¹¹ demonstrated gonococci in the endometrium eight to fourteen days (in one case already five days) after contact. Jaschke and Pankow¹² describe gonorrhea with menstrual disturbances as an outstanding symptom.

Summary

Three hundred seventeen cases of gonorrhea in women are presented. These represented 13.8 per cent of all new cases entering a gynecology clinic for varying complaints in one year.

The most frequent symptom complained about in this group was abdominal pain.

Almost one-fourth of the patients presented themselves because of menstrual disturbances. Stress is laid upon this symptom in early gonorrhea.

Bacteriologic examination of women with a history of menstrual disturbances is urged.

edema as well as generalized edema are due in a large part to low serum protein levels.²²

The administration of plasma to increase the osmotic pressure of the circulating blood is physiological. According to Best and Taylor,⁴ the osmotic pressure of the plasma increases as the blood passes along the capillary, as a result of the passage of water outward and a consequent rise in concentration of protein. That is, the force holding fluid within the vessel is increased. By adding to the existing serum protein this effect will be increased, and if the plasma proteins are reduced, as they are in most severe toxemias, there will be an excess of fluid in the tissue spaces because the effective osmotic pressure is diminished.^{8, 16, 18, 19, 25, 26}

In toxemias of pregnancy it has been shown that there is a diminished blood volume, hemoconcentration, and hypertension. When the filtration pressure is increased (hypertension) and is associated with a diminished colloidal osmotic pressure, the flow of urine should be increased. This is not the case in toxemias where the effective filtration pressure is not in force due to a generalized vasoconstriction which will include the afferent vessels of the glomeruli.⁴ The addition of concentrated plasma will alter this condition²⁷ to the extent of increasing the circulating blood volume, decreasing viscosity, and rendering the blood more easily filterable by the glomeruli.

Concentrated plasma is used merely as an adjunct to the usual treatment. Hypertonic glucose solutions cannot be dispensed with.²⁶ These are considered to be truly diuretic in contradistinction to the action of plasma which brings about a *sustained increase* in blood volume.^{11, 19} Glucose solutions are often the only source of nutrition for the comatose patient, and possibly protect the liver parenchyma against further damage as well as aid in regeneration of damage to the liver. Sedation is indicated in fulminating rises in blood pressure and nervous irritability.

We have found that less sedation is required after the administration of concentrated plasma. Concentrated plasma does not bring about a marked increase in urinary output in a patient without edema.

Concentrated plasma should not be given with impunity. Overloading of the circulatory system is easily brought about in patients with a tendency to right heart failure.¹¹ It has been shown that relatively large amounts of concentrated plasma given rapidly to small animals with diminished lung tissue can readily produce fatal pulmonary edema.⁹ It is for this reason that we have been using only twice concentrated plasma to prevent the possibility of introducing fluid too rapidly into the circulatory system before urinary excretion and compensation by the vascular bed can take care of the added burden. If this should happen in the course of therapy, phlebotomy is advocated.^{2, 11} We have not had to resort to this procedure. Reactions other than pulmonary edema have been noted. In ten thousand plasma transfusions Miller and Tisdall¹⁷ noted 258 mild reactions which were classified as thermal and allergic. A near fatal reaction has been reported by Polayes and Squillace.²¹ We have had one mild thermal reaction.

Summary

1. Concentrated plasma is a potent therapeutic agent as an adjunct in the treatment of severe late toxemias of pregnancy.

CONCENTRATED PLASMA IN THE TREATMENT OF THE SEVERE LATE TOXEMIAS OF PREGNANCY

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THE use of colloidal substances to increase the osmotic pressure of the blood and effect clearing of edema and produce diuresis is not new. Dieckmann,⁵ in 1931, had this principle in mind when he reported the use of 6 per cent gum acacia in severe eclamptics, with good results. His aim was to obtain a sustained blood dilution not attainable with hypertonic glucose. Dexter and Weiss suggested the trial of concentrated plasma, serum, or albumin.^{6, 7}

It has been shown that there is an alteration in protein metabolism (in the liver) which begins about the third lunar month in approximately 75 per cent of apparently normal pregnancies, causing a reduction of the serum protein level. This in turn predisposes to edema.²³

We are primarily interested in alleviating anuric and convulsive manifestations of severe toxemias of pregnancy which often terminate fatally. These findings so commonly occur together that for all practical purposes we can consider them as one, and by relieving edema and convulsions, death may be prevented. That diuresis is important will not be questioned. The most reliable sign of improvement has been diuresis, and until diuresis occurs, improvement has rarely taken place.⁶

We feel that concentrated plasma is the answer to this problem. The senior author first used concentrated plasma in 1941 in a severe eclamptic with spectacular results. Upon checking the literature at that time, little was found on the use of concentrated plasma in the late toxemias of pregnancy.

Concentrated plasma has been used in other specialties for the reduction of edema. Hughes and co-workers¹³ used it to reduce intracranial pressure. They were able to reduce the cerebrospinal fluid pressure from 300 to 100 mm. of water in seventeen hours with 100 c.c. of four times concentrated plasma. Concentrated plasma has been used often to reduce the edema in nephrosis in children by Aldrich,¹ Jeans,¹⁴ and Hill.¹⁰ Reduction of edema has been brought about by the use of normal plasma in intestinal surgery by Ravdin and associates.²⁴ Beneficial results have been obtained with the use of four times concentrated plasma in edema of the upper respiratory tract.⁶ Pooled serum has been used in obstetrics with excellent results by Benaran and Farnsworth³ to stimulate diuresis in one severe eclamptic after hypertonic glucose and magnesium sulfate had failed. Hill,¹² in 1940, used 300 c.c. of four times concentrated plasma in an eclamptic in order to correct a low serum protein.

One of the most common and serious complications of the late toxemias of pregnancy is cerebral edema and/or hemorrhage. In a review by Parks²² these conditions of the brain were a constant postmortem finding. It has been the authors' experience to find brain damage in the absence of the classically described liver of eclampsia. There seems to be little doubt that cerebral

per cent glucose and 500 c.c. of 20 per cent glucose were given. An indwelling catheter was inserted, and the urinary output was found to be 2,290 c.c. for twenty-four hours.

On October 31 her temperature was 101.4° F. (ax), pulse, 140, respirations 30, blood pressure 250/130. The patient had three convulsions. Luminal grains iii, MgSO_4 20 c.c. of 10 per cent (i.v.), $3\frac{3}{4}$ grains sodium amytal (i.v.), 400 c.c. of 10 per cent glucose and 500 c.c. of 20 per cent glucose were given. Total output for the day was 845 c.c., and condition was regarded as poor.

On November 1 the patient's temperature was 98.6° F., pulse 90, respirations 98.6, blood pressure 200/120. Morphine and hypertonic glucose solutions were continued. Patient had no further convulsions.

Daily intravenous, hypertonic glucose and morphine were given for four days. The patient's condition remained unchanged, and the urinary output remained adequate.

On November 6 two disturbing manifestations were noted: the urinary output was reduced to 750 c.c. for twenty-four hours, and the patient had severe epistaxis. Hypertonic glucose was again given with no increase in urinary output. Concentrated plasma (300 c.c.) was given and urinary output increased to 1,600 c.c.

On November 7 the membranes were stripped in an attempt to induce labor. The output was 3,700 c.c. for this 24-hour period.

On November 8 the patient delivered a premature stillborn infant spontaneously.

On November 12 the patient deserted but had no edema. Her blood pressure was 180/100; a three plus albumin was present, and her serum proteins were 6.51.

CASE 3.—Mrs. C. D. B. (T-46-214342), aged 23 years, primigravida, was admitted Nov. 19, 1946, having had no prenatal care. Expected date of confinement was Dec. 29, 1946. On admission her blood pressure was 190/130 with no demonstrable edema. Urine showed three plus albumin; serum proteins 4.7, hematocrit 45, hemoglobin 14.1 Gm., and a red blood count of 5,050,000. The patient was not in labor, so was transferred to the prenatal ward for "toxemia care." Urinary output was 1,250 c.c. for first twenty-four hours and remained adequate.

On November 22 the patient's blood pressure was 200/140, and urinary output was reduced to 650 c.c. for twenty-four hours. Fifty cubic centimeters of 50 per cent glucose and 20 c.c. of 10 per cent MgSO_4 were given intravenously with no improvement. Three hundred cubic centimeters of twice concentrated plasma were given with prompt increase in urinary output to 2,375 c.c. for the next twenty-four hours.

On November 23 the patient delivered, with low forceps under pudendal block, a living male infant weighing 5 pounds, 14 ounces.

Her condition steadily improved, and she was discharged on the thirteenth postpartal day, with a blood pressure of 140/100, no albuminuria, and a serum protein of 5.81.

CASE 4.—Mrs. M. V. (I-45-195334), aged 20 years, Negro, primigravida, was first seen in prenatal clinic on April 17, 1946. Her prenatal course was benign except for occasional headaches. Blood pressure was within normal limits, and only on the last two visits was a one plus pedal edema noted.

On November 4 the patient was admitted with mild pains, blood pressure 138/84, two plus albuminuria, and no edema. Labor ceased shortly after admission; therefore she was transferred to prenatal ward for "toxemia care."

2. The colloidal osmotic action exerted by plasma is physiological. (a) It reduces edema; (b) re-establishes normal concentration of blood; (c) re-establishes circulating blood volume; and (d) increases urinary output.

3. By virtue of a decreased blood volume, toxemic patients are prone to go into vasomotor collapse following small hemorrhages. Lambeth¹⁵ has shown that concentrated plasma will help prevent this untoward complication.

4. In the absence of edema, concentrated plasma has little effect on urinary output.

Case Reports

There has been no definite routine in handling any of the severe toxic patients at Charity Hospital. These patients were handled by three different services. The usual treatment of forcing fluids (intravenously or by mouth), sedation, careful check of urinary output, and watching for an optimal time for induction has been followed. Concentrated plasma was used upon the suggestion of the authors when all therapy had apparently failed and the patient's condition was not improving or was becoming more precarious.

CASE 1.—K. B., aged 19 years, primigravida, was admitted to a home for wayward girls Sept. 19, 1941, complaining of severe headaches. Expected date of confinement was Oct. 1, 1941. Blood pressure was 190/170; the urine boiled solid. Examination: marked edema of extremities and face. Edema of eyelids was so marked they could not be opened. Treatment: morphine for nervous irritability, and hypertonic glucose infusions. The output was not recorded.

On September 20 the patient's temperature was 102° F. (ax), pulse 140, and respirations 30. Patient had one convulsion controlled by intravenous sodium amytal, followed with seconal and hypertonic glucose solutions. On examination it was found she was in labor and the presentation frank breech. Urinary output for this 24-hour period was 130 c.c. Condition was regarded as critical.

On September 21 a viable male child was delivered. Patient's condition remained unchanged. Urinary output was 60 c.c. for this 24-hour period.

On September 22 the patient's condition remained critical. In spite of hypertonic glucose therapy, the urinary output was 260 c.c. Concentrated plasma was given with almost immediate dramatic results. The following 24-hour period showed a urinary output of 3,470 c.c.

Her condition improved and the urinary output continued good. She was discharged on her fifteenth postpartal day with a normal blood pressure and no albuminuria.

Serum protein determinations were not available at this institution, and the specimen of blood was lost enroute to laboratory.

CASE 2.—Mrs. J. M. H. (L-227804), aged 19 years, primigravida, was admitted Oct. 30, 1946, from prenatal clinic. Expected date of confinement was Jan. 8, 1947. During prenatal care, blood pressure was 145/100 with no albuminuria. Admission notes: marked edema of extremities and face; fundal examination revealed papilloedema with hemorrhage; blood pressure was 245/170, pulse 90, temperature 98.6° F. and respirations 25. Several hours after admission blood pressure was recorded at 190/100, and urine showed a four plus albumin with red blood cells and a few finely granular casts; serum protein 5.46, hematocrit 43, hemoglobin 14 grams, and red blood count 4,500,000. Patient was irritable. Treatment: morphine, an infusion of 1,000 c.c. of 10

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On November 6 the blood pressure was 160/120, blood urea nitrogen 23.5, serum protein 4.7, and hemoglobin 13 grams. Patient was sedated with luminal and given hypertonic glucose infusions.

On November 8 the albuminuria was three plus.

On November 9 the albuminuria was four plus. Patient was in labor, and urinary output dropped sharply to 200 c.c. for an eight-hour period. Three hundred cubic centimeters of twice concentrated plasma were given. The urinary output was 350 c.c. for the next two hours. This was followed by a second unit of concentrated plasma, and after an eleven-hour labor a living male infant weighing five pounds and three ounces was delivered with low forceps under local anesthesia. Urinary output was sustained to a total of 2,200 c.c. for the remainder of the day. The urinary output for three days postpartally was 3,500, 4,950, and 5,350 c.c., respectively.

On November 18 the serum proteins were 6.16.

The patient was discharged after eighteen days hospitalization, in good condition with no albuminuria, blood pressure 125/88, and no complaints.

CASE 5.—E. P. (L-46-247981), aged 18 years, Negro, primigravida, was admitted on Dec. 31, 1946, with a history of 12 to 14 major convulsions during the previous sixteen hours. She had been treated by a private physician for syphilis. For the preceding two weeks dizziness, swelling of the feet, vomiting, and severe headaches were present, and the patient consulted the doctor, who advised that the blood pressure was high. Following the convulsions, a hypodermic was given and patient sent to Charity Hospital.

On admission, the patient was drowsy but could answer questions. Blood pressure was 128/82. Examination: fetal heart tones were present, and a one plus edema of extremities. Urinalysis showed three plus albuminuria and numerous casts. Blood examinations revealed positive serology, serum proteins 4.7, hemoglobin 11.75 Gm., and a red blood count of 4,090,000. Treatment: 2,000 c.c. 10 per cent glucose and 1,000 c.c. 20 per cent glucose were given after which edema increased. Patient became comatose, and pulmonary edema developed. Blood pressure rose to 150/115, and urinary output was 650 c.c. for the night. Fifty cubic centimeters of 50 per cent glucose relieved the pulmonary edema, and the patient became responsive.

On January 1, 300 c.c. of two times concentrated plasma were given when oliguria became severe (150 c.c. in eight hours). Response was immediate and dramatic from practically no output to twenty-four drops per minute. Output was sustained for twenty-four hours at a rate of 600 to 800 c.c. per eight-hour periods.

On January 2 concentrated plasma was repeated with less dramatic results. Blood pressure rose to a maximum of 180/136. Urinary output was 300 to 500 c.c. for eight-hour periods.

On January 3 a third unit of concentrated plasma was given with a minor febrile reaction. For this reason no further plasma was given. Total twenty-four hour output was 600 c.c.

On January 5 the output was 1,775 c.c., fetal heart tones were not heard.

On January 6 the patient delivered a premature, macerated fetus. Urinary output was 2,525 c.c.

Patient steadily improved and was discharged January 22 in good condition with no edema, blood pressure 115/75, no albuminuria, and a serum protein of 5.81.

We wish to acknowledge our appreciation to Dr. Adolph Jacobs and Dr. D. W. Goldman for use of cases on their services.

larger. At that time the last blood study was Oct. 2, 1946, which showed 10.2 Gm. hemoglobin. At this visit the hemoglobin was 6 Gm. with 1,630,000 red blood cells and 2,000 white blood cells. There were 66 segmented neutrophils, 8 stabs, and 26 lymphocytes. The patient was sent directly to the hospital for transfusion and study.

A transfusion of 500 c.c. bank blood was given the afternoon of admission, and another 1,000 c.c. given the next day. While the last transfusion was being given the patient went into labor spontaneously. It was noted that she had a heavier than normal bloody show. After a labor of approximately ten hours she delivered a normal 6 pounds, 8 ounces male baby. The placenta separated spontaneously within four minutes, and the uterus contracted nicely with very little bleeding from the uterine cavity. Episiotomy was not done. The cervix bled from several small abrasions and there was a constant oozing from a first degree laceration of the vagina. Suture and compression failed to control this bleeding after an hour's time. Vitamin K was given empirically, and finally another 500 c.c. transfusion of blood before the patient left the delivery room. Transfusion and vaginal pack apparently controlled the bleeding after about three hours.

The patient's temperature was 100° F. on admission to the hospital. It went to 101.2° F. after three hours' hospitalization and rose to 101.8° F. during labor. Within four hours after delivery the temperature was 104° F. and the patient had no complaints. From that time until the sixth postpartum day the temperature ranged between 100° and 104° F. It returned to normal the same day that the red cell count first reached 4,000,000. No evidence of infection of any type could be demonstrated during the course of high fever. There was a moderately severe diarrhea which checked when the temperature and blood picture returned to normal. The stools were negative for gross and occult blood and for ova and parasites.

Postpartum Physical Examination.—On the first postpartum day, examination revealed a very pale and weak white female who appeared older than the given age. The conjunctiva, lips, and nail beds were almost white. Ophthalmoscopic examination revealed only a pale retina—no area of hemorrhage.

There were some doubtful purpuric spots over the roof of the mouth. Several shallow grayish ulcers were seen beneath the tongue and along the lower lip and gum.

A few small submaxillary lymph nodes were palpated, but there was no generalized lymphadenopathy.

Chest examination revealed nothing more than a soft systolic murmur in the pulmonic area.

On palpation of the abdomen the liver was definitely felt one to two fingerbreadths below the right costal border. The spleen could not be palpated. No other organs or masses than a first day postpartum uterus were felt.

Extremities were negative. Reflexes were bilaterally equal, and no abnormal skin sensitivity was demonstrated.

Four days after this examination multiple purpuric spots appeared over the neck, thorax, abdomen, and upper thighs. During the same period there was bleeding from the nose but with very little blood loss. The liver was not palpable after the third postpartum day.

Therapy.—Penicillin in 20,000 unit doses was given intramuscularly every three hours from the time of delivery until recovery. This was done with the thought of preventing infection during the time when the white and red cells were at such a low level.

Concentrated liver extract 2 c.c. intramuscularly daily was started on the third postpartum day. Pentnucleotide was started, but had to be discontinued after the second injection because of systemic reaction.

CLINICAL AND HEMATOLOGIC APLASTIC ANEMIA WITH HYPERCELLULAR MARROW IN PREGNANCY

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THE total number of cases of this type of anemia found with pregnancy is apparently very small. However, it has occurred often enough to suggest that the term "idiopathic" may no longer be fitting. Indeed, this report is being made to offer much-needed evidence that this disease may, in rare instances, be caused by pregnancy.

Several possible specific etiologic factors have been suggested, but the rare occurrence makes it likely that the actual cause will remain hypothetical for years to come. That an aplastic peripheral blood picture with pregnancy is not coincidental is reasonable but still equivocal.

Case Report

Mrs. M., a 27-year-old gravida iv para iii of Irish, French, and Indian descent, was first seen when three months pregnant. At that time she had a hemoglobin of 10 Gm. and total white cell count of 7,000. The blood was negative for syphilis and was RH positive.

First Pregnancy.—1940—As a primigravida the patient went to term without complications. There was an easy delivery of a normal baby and an uneventful postpartum course.

Second Pregnancy.—1942—Went to term without complications. Following delivery temperature went to 103° F. on one occasion, but returned to normal in thirty-six hours. Routine blood study at that time showed hemoglobin 60 per cent, red blood count 3,450,000, white blood count 5,200 with 76 per cent neutrophils, 23 per cent small lymphocytes, and 1 per cent eosinophiles.

Third Pregnancy.—1944.—Prenatal course was apparently normal until shortly before delivery. A few days before labor the patient developed diarrhea and fever. She gave a history of excessive bleeding at delivery. Routine blood study at that hospital admission revealed 6.8 Gm. hemoglobin, red blood count 2,000,000, white blood count 2,000.

Patient had a continued high fever while in the hospital and stated she "went home to die" on her fifth postpartum day with a temperature 103° F. She continued to have diarrhea, high fever, and numerous ulcers of the mouth for two months. During that time she had no medical care whatever. After two months she made a spontaneous recovery but remained weak for several weeks longer. She remained in excellent health following recovery until the onset of the present illness.

Fourth Pregnancy.—1946—With this last pregnancy the patient had a normal prenatal course until sixteen days before she delivered. At that time, Oct. 31, 1946, she came to the office complaining of several small ulcers of the mouth beneath the tongue. Local treatment was given and slight subjective improvement noticed. Five days after that office visit the patient began to bleed a little from the anus at the time of bowel movements.

The patient presented herself at the office again on Nov. 13, 1946. At this visit she was extremely pallid and weak. There was evidence of bleeding from anal fissures, and the patient stated that it had been fairly constant with an alarming total loss of blood. The ulcers of the mouth were more numerous and

Blood transfusion was the chief form of therapy. Ten 500 c.c. transfusions were given, but one was discontinued before completion because of a pyrogen reaction.

TABLE II. ADDITIONAL LABORATORY DATA

| | URINE | ALBUMIN FT TR, SUGAR FT TR, PUS CELLS 20-30 L.P.F., BACT. LOADED |
|----------|------------------|--|
| 11/16/46 | Agglutination | Negative in all dilutions for typhoid "O" and "H" Paratyphoid "A" and "B" Proteus "ox 19," and B-abortus |
| 11/18/46 | Clot retraction | Not begun in 24 hours |
| 11/18/46 | X-ray | E.P.A. view of chest negative |
| 11/18/46 | Fragility test | 42% beginning of hemolysis, 32% complete hemolysis |
| 11/18/46 | Icterus index | 12.5 units per 100 c.c. serum |
| 11/20/46 | Serum biliruben | 1.3 mg. per 100 c.c. serum |
| 11/22/46 | Feces | Occult blood negative; no ova or parasites found |
| 11/23/46 | Biopsy | Sternal bone marrow hypercellular |
| 11/30/46 | Gastric analysis | No free HCl, total acidity 9 |

Discussion

According to Rhoads and Miller¹ "hypercellularity of the marrow has been a particular common observation in those instances in which certain chemical substances could be identified as causative of the anemia." They cited Turnbull's findings of hypercellularity in trinitrotoluene poisoning, Anderson's in benzene poisoning and Martland's in radium poisoning.

Assuming that some by-products of pregnancy suppress the bone marrow in these cases it seems logical to expect a picture similar to that resulting from known extraneous poisons, especially when the clinical picture is of short duration.

It is regrettable that a marrow study was not made in this case when the peripheral blood showed the most severe reduction in all elements. Since the sternal biopsy was taken on Nov. 23, 1946, at which time hematologic and clinical improvement had taken place one can only guess what an earlier biopsy would have shown. However, that a marrow may change from one "very poor in cells" to one described as "cellular" in a period of four days is well proved in the case of Nieuwenhuis, cited by Hurwitt and Field.²

Summary

This case is significant because of the occurrence of a similar illness at about the same time in the last two pregnancies. In each case there was complete recovery following relatively prompt delivery. The recovery in the second instance was thought to be more rapid simply because the condition was recognized and treated intensively by blood transfusion.

No attempt is made to classify this as a true aplastic anemia in the strictest sense of the term. A more fitting title, as put forward by Bamford and Rhoads,³ would be refractory anemia with hypercellular marrow.

It is felt that this case offers evidence of a causal relationship between pregnancy and an aplastic peripheral blood picture because of the above-mentioned course of the disease and the total absence of symptoms when the patient was not pregnant.

References

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3. Bamford, R. R., and Rhoads, C. P.: Quart J. Med. 10: 175, 1941.

TABLE I

| DATE | TRANS- FUSION | HEMO- GLOBIN (GM.) | RED BLOOD COUNT | WHITE BLOOD COUNT | SEG. (neut.) | STAB | LYMPHO- CYTES | MONO- CYTES | EOSIN- OPHILES | PLATELETS | RETICULO- CYTES | |
|-----------------|------------------|--------------------------|-----------------------|-------------------------|-----------------|------|------------------|----------------|-------------------|------------------|--------------------|---|
| 1942 | | 10.2 | 3,450,000 | 5,200 | (neut.) 76 | | 23 | | 1 | | | Delivery of second baby. Temp. 103.8° F. one reading. Nor- mal in 36 hours |
| March, 1944 | | 6.8 | 2,000,000 | 2,000 | | | | | | | | Delivery of third baby. Tem- perature elevation for 2 months; confined to bed for 4 months |
| 5/30/46 | | 11.5 | | 7,200 | | | | | | | | Prenatal visit to office. Patient 3 months pregnant |
| 10/ 2/46 | | 10.2 | | | | | | | | | | 8 months pregnant |
| 11/13/46 | 500 c.c. | 6.0 | 1,630,000 | 2,000 | 66 | 8 | 26 | | | | | 9 months pregnant. Admitted to hospital |
| 11/14/46 | 1,000 c.c. | 7.8 | 2,310,000 | | (neut.) 40 | | 60 | | | | | Delivery |
| 11/15/46 | 500 c.c. | 10.2 | 2,970,000 | 4,100 | | | | | | | | |
| 11/16/46 | 500 c.c. | 8.5 | 2,670,000 | 600 | 33 | 18 | 43 | 1 | | None seen | 1.6% | First postpartum day |
| 11/18/46 | | | | | (neut.) 27 | | | | | 92,000 | 0.3% | Third postpartum day |
| 11/19/46 | 500 c.c. | | | | (neut.) 42 | | 58 | | | | | Fourth postpartum day |
| 11/20/46 | 1,000 c.c. | 10.5 | 2,920,000 | 1,250 | | | | | | | | Fifth postpartum day |
| 11/21/46 | | 12.9 | 3,760,000 | 1,250 | | | | | | | | Sixth postpartum day |
| 11/22/46 | | 11.5 | 4,120,000 | 1,500 | 27 | 20 | 35 | | 3 | 26,320 40,000 | 0.6% | Seventh postpartum day |
| 11/23/46 | 1,000 c.c. | | | | (neut.) 62 | | 38 | | | 167,600 | | Eighth postpartum day |
| 11/25/46 | | 14.3 | 4,190,000 | 5,400 | | | | | | | | Tenth postpartum day |
| 11/27/46 | | 14.6 | 4,520,000 | 6,750 | (neut.) 76 | | 24 | | | | | Twelfth postpartum day |
| 11/29/46 | | 16.2 | 4,830,000 | 7,700 | (neut.) 78 | | 21 | | 1 | | | Fourteenth postpartum day |
| 1/16/47 | | 12.5 | 4,420,000 | 7,450 | 63 | 5 | 25 | 5 | | | | Sixty-second postpartum day |
| Baby's blood | | 18.0 | 5,440,000 | 5,150 | (neut.) 32 | | 64 | | 2 4 | 200,000 | | |

After her discharge from the hospital in 1939 the patient was followed in the outpatient department. She complained at various times of headaches, palpitation, and such visual disturbances as scotoma and transient blindness. She was treated with phenobarbital.

The patient's sixth admission was on March 22, 1943, when she complained of severe headache, radiating from the occipital to the frontal region of the head. Examination showed the neck to be slightly stiff, and the pupils of the eyes were pinpoint and did not respond to light or accommodation. A lumbar puncture was done; the cerebrospinal fluid was grossly bloody, and the initial pressure of the fluid was 400 millimeters of water. Microscopic examination showed 42,000 red blood cells and 50 white blood cells per cubic millimeter; proteins were 11 per cent.*

Serial lumbar punctures were done, and on the twelfth hospital day the pressure of the spinal fluid was normal and the patient was discharged on April 10, 1943.

Diagnosis.—Subarachnoid hemorrhage due to a miliary aneurysm of the Circle of Willis.

The patient was next admitted on November 11, 1944. One week before she began to have headaches, pain in the left eye, and some swelling of the globe of this eye. The day before admission she became unconscious for three hours and, when she awoke, she had severe headache, a stiff neck, and she vomited several times.

During examination she was extremely lethargic. Her temperature was 37.4° C., pulse 72, respirations 20, and blood pressure 144/82. The pupils were contracted and there was a medium-sized round hemorrhage in the temporal portion of the left eye. The heart was slightly enlarged to the left; rhythm was normal, with a bradycardia, and a harsh systolic murmur was heard at both the apex and the base. The cerebrospinal fluid was grossly bloody; the initial pressure was over 350 millimeters of water and the final pressure was 150 millimeters.

The patient improved after lumbar punctures and on the third day the spinal fluid was nearly clear and had an initial pressure of 250 millimeters of water and a final pressure of 120 millimeters of water. She was discharged on Dec. 1, 1944.

Diagnosis.—Recurrent rupture of an aneurysm of the Circle of Willis, due to congenital arterial hypoplasia.

The patient was readmitted on Feb. 4, 1945. She was about three months pregnant, and was admitted for consideration of a therapeutic abortion. She was having occasional frontal headaches. On examination, a moderately harsh blowing systolic murmur was heard over the entire precordium which was loudest at the apex. The blood pressure was 110/70.

A consultation was held with several physicians in regard to a therapeutic abortion, and it was decided not to perform one, but that the patient should be sterilized forty-eight hours after delivery.

The patient was admitted to the obstetric service on April 4, 1945, in a semicomatose condition. With rest, she felt better, but on the morning of April 7 she had a generalized convulsion, became comatose, and had pulmonary edema. She was transferred to the medical service. Her temperature was 38.8° C., pulse 66, respirations 14, and blood pressure 210/180. The pupils reacted sluggishly to light; the left pupil was larger than the right, and there was slight papilledema bilaterally with several large hemorrhages, remote and recent. The neck was stiff and there was a constant motion of the right arm. A positive Kernig reaction was obtained. Numerous loud coarse rhonchi were heard

*As reported by laboratory.

CONGENITAL ANEURYSM OF THE CIRCLE OF WILLIS ASSOCIATED WITH PREGNANCY

E. E. RHOADS, M.D., CINCINNATI, OHIO

(From the University Hospitals of Cleveland)

CASE 1.—W. S. was admitted to the hospital for the first time on June 22, 1932. Three days before entrance she had had a sudden attack of dizziness and fainting, and became unconscious for thirty minutes. When she regained consciousness she had a severe generalized headache and a feeling of numbness in the left side of her face, left arm, and left leg. There was no loss of function in any of these areas.

During the physical examination the patient was extremely restless and had Cheyne-Stokes' respiration. Her neck was slightly stiff. There was a questionable systolic murmur at the apex, and a blowing systolic murmur at the base. The left border of cardiac dullness was ten centimeters from the mid-sternal line. There was a suggestive positive Kernig test on the right side, and no Babinski reaction. The temperature was 37.5° C., pulse 66, respirations 36, and blood pressure 125/75. The cerebrospinal fluid was grossly bloody, the pressure was 550 millimeters of water, Pandy reaction was four plus, and the fluid was loaded with red blood cells; a smear of the spinal fluid sediment showed many polymorphonuclear leucocytes and many lymphocytes.

The lumbar punctures were repeated daily and on July 2, 1932, the cerebrospinal fluid showed a pressure of 190 millimeters of water and was clear. The Pandy reaction was one plus, and the cell count was only 13. The patient kept improving and was discharged July 7, 1932.

Diagnosis.—Meningeal hemorrhage.

The patient was readmitted to the University Hospitals on June 25, 1934, complaining of a severe sore throat and of a swollen, painful right knee. She gave an indefinite history of rheumatic fever at the age of 16 years.

The physical examination showed large, boggy tonsils with a moderate amount of purulent exudate. There were several small discrete nontender lymph glands in the neck. There was no abnormal precordial activity. The blood pressure was 120/70. The right knee was hot, swollen, painful on motion, and contained a large amount of fluid.

An electrocardiogram showed delayed interventricular conduction. A sedimentation rate was 2.7 millimeters per minute, and this dropped to 1.6 millimeters before discharge. The patient was given salicylates and was able to be discharged on July 4, 1934.

Diagnosis.—Acute rheumatic fever.

The patient was readmitted to the hospital on Sept. 5, 1934, complaining of chills accompanied by fever, painful respirations, and a cough. Her temperature was 40.2° C., pulse 120 and respirations 40, blood pressure 115/80. A diagnosis of lobar pneumonia was made. Antipneumococcal serum, type 1, was given, and the patient improved and was discharged on Sept. 25, 1934.

Diagnosis.—Pneumococcal lobar pneumonia, type 1, questionable acute rheumatic fever.

The patient was again admitted to the hospital on Aug. 3, 1936. She had a tonsillectomy performed. Her fifth admission was on Sept. 18, 1939, when she had to have an appendectomy. Her condition was satisfactory following both of these operations.

Comment

Congenital aneurysms of the Circle of Willis usually show few signs or symptoms until they rupture. About 50 per cent of the cases end fatally. In the series reported by Richards and Hyland, uncomplicated pregnancy was considered insignificant as a precipitating factor. However, in our first case, there are four factors that must be considered in the sequence of the five attacks of subarachnoid bleeding which resulted in the death of the patient:

1. In any pregnancy there is an increased volume strain on the vascular system.

2. The blood flow through the brain is not decreased during sleep.⁵

3. With each hemorrhage the damage done to the vessel makes it more vulnerable for subsequent bleeding.

4. Hypertension.

Hypertension is frequently present in patients with ruptured aneurysms and is probably the pre-existing condition most often found. Patients who have had vascular accidents should not have another pregnancy, because of the possibility of cardio-vascular-renal damage which is present during every pregnancy. The pressure of the fundus of the uterus on the renal vessels has been known to elevate the blood pressure.⁶

Headache is the most common symptom of intracranial hemorrhage. In patients with intracranial lesions the signs of vertigo, numbness, weakness, visual disturbances, unconsciousness, convulsions, and hemiplegia vary according to the extent and severity of the hemorrhage. Bloody spinal fluid is of utmost diagnostic importance. Many patients, without premonitory symptoms or signs, die within a short period of time.

We believe that, when a patient has had a subarachnoid hemorrhage from a ruptured congenital aneurysm or any vascular accident, contraceptive means should be used to prevent future pregnancies which are certain to be dangerous to the patient. If a cerebral hemorrhage has occurred during an early gestation period, sterilization should be carried out under local anesthesia as soon as the patient's condition permits.

Summary

1. Two cases of congenital aneurysms of the Circle of Willis associated with pregnancy have been presented.

2. The seriousness of such vascular lesions has been shown by statistical reports; the prognosis should always be guarded.

3. If a patient has a past history of hemorrhage from the rupture of an intracranial blood vessel, future pregnancies must be prevented, preferably by sterilization.

4. Pregnancy adds gravity to the prognosis because of the increased blood volume; the increased pressure of the uterus on renal vessels, and the increased strain during labor.

5. Termination of pregnancy is justified in all cases of proved bleeding from intracranial aneurysms.

I wish to thank Dr. Roscoe Leas and Dr. E. P. Kennedy for permission to report Case 2.

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throughout the chest. The heart was enlarged to the anterior axillary line, and there was a systolic murmur at its apex. The uterus was two fingerbreadths above the umbilicus.

The spinal fluid showed an initial pressure of over 350 millimeters and contained 2,500,000 red blood cells per cubic millimeter; proteins were 460 milligrams per cent and the platelet count was 350,000. The blood urea nitrogen was 33 milligrams per cent; serum protein 7.7 Gm.; albumin 3.8 Gm., and globulin 4.8 grams.

The patient did not regain consciousness and died of respiratory failure on April 9, 1945. An autopsy was performed and the final diagnoses were:

1. Congenital "berry" aneurysms of the Circle of Willis.
2. Bilateral bronchopneumonia with partial atelectasis of lower lobes of both lungs.
3. Hypertrophy and dilatation of the heart.
4. Gravid uterus.

CASE 2.—G. S. This patient, 27 years old, was delivered of a baby at University Hospitals on April 12, 1944. She was discharged on April 20, 1944, apparently in good condition. Her stay in the hospital was uneventful except for headaches which were on the right side and in the occipital region. On April 21, 1944, she had several generalized convulsions at home and was readmitted to the hospital.

A lumbar puncture showed clear, colorless cerebrospinal fluid, with an initial pressure of 210 millimeters of water; the microscopic examination showed 200 red blood cells and 5 white blood cells per cubic millimeter. On April 25, the patient had convulsions which began in the fingers of the right hand, spread up the right arm, involved the face, and then became generalized. She had some papilledema. She was transferred to the medical service on April 26, 1944. Her temperature was 38.8° C., pulse 70, respirations 18, and blood pressure 130/80. Examination revealed slight horizontal nystagmus, stiffness of the neck, and hyperactive reflexes. The Brudzinski sign was positive on the left side; the Gordon-Holmes sign was positive on the right side. The cerebrospinal fluid was grossly bloody and had an initial pressure of 320 millimeters of water and a final pressure of 150 millimeters of water. The Pandy test was 2 plus; red blood cell count was 12,000 per cubic millimeter, and white blood cell count was 30 per cubic millimeter, with polymorphonuclear cells predominating; proteins were 66.8 milligrams per cent. A culture of the spinal fluid showed no growth of microorganisms.

On May 5, 1944, a lumbar puncture showed an initial pressure of 350 millimeters of water and a final pressure of 110 millimeters of water, and yielded 6 cubic centimeters of xanthochromic fluid. There were 1,300 red blood cells and 5 white blood cells per cubic millimeter; proteins were 59.2 milligrams per cent.

The patient continued to have mild convulsions for two or three days with occasional nystagmus. On May 5, 1944, she developed what was thought to be a venous thrombosis of the left femoral vein. Her condition improved after rest in bed and repeated lumbar punctures and she was discharged on May 17, 1944.

Diagnoses.—Meningeal hemorrhage, probably from rupture of congenital aneurysm of the Circle of Willis. Thrombophlebitis of left femoral vein.

Botsford, Thomas W., and Kinney, Thomas D.: Acute Salpingitis Due to Friedländer's Bacillus, *New England J. Med.* 235: 539, 1946.

The authors give a case report of an 80-year-old woman, with acute suppurative salpingitis due to Friedländer's bacillus. The bacillus was recovered from the sputum, peritoneal cavity, fallopian tube, and a postoperative wound abscess.

It is suggested that the lungs were the primary focus of infection. JAMES P. MARR.

Newborn

Wiener, A. S., and Wexler, I. B.: The Use of Heparin When Performing Exchange Blood Transfusions in Newborn Infants, *J. Lab. & Clin. Med.* 31: 1016-1019, 1946.

The authors describe a simple technique they use to overcome the main obstacle to the successful performance of an exchange transfusion in infants—i.e., the problem of coagulation of infant blood upon withdrawal. This problem was circumvented by using heparin, cutting down upon several arteries, and replacing 500 c.c. via the saphenous vein. The authors admit that during "one short period the infant became pale and showed evidence of air-hunger," but concludes that their procedure might be indicated in severe cases of icterus gravis. Nine of the ten references are those of the senior author. C. E. FOLSOME.

Gruber, Seymour, Litvak, Abraham, and Jacobi, Mendel: A Case of Erythroblastosis Fetalis Caused by Isoimmunization With the Agglutininogen B, *J. Pediat.* 29: 518, 1946.

A case of erythroblastosis fetalis caused by isoimmunization of an Rh-positive, type O mother by a type B baby is reported with confirmatory blood serologic findings.

It is suggested that when an erythroblastosis infant is seen, whose mother is type O and her Rh factor unknown, the baby be transfused with type O Rh-negative blood. This would obviate the possibility of giving the infant blood to which he has circulating isoagglutinins. JAMES P. MARR.

Cohen, Philip, and Scadron, Samuel J.: The Effects of Active Immunization of the Mother Upon the Offspring, *J. Pediat.* 29: 609, 1946.

The authors in this well documented paper suggest an addition to prenatal care. They assert that deficiencies in immunity against diphtheria, pertussis, or any remediable infection which may be endemic may be corrected by appropriate combined immunization of the mother during pregnancy.

Apparently, as a result of childhood prophylaxis, women today lack immunity to diphtheria in about 50 per cent of cases, in contrast to 85 per cent immunity in the preimmunization era of the past generation. Also that about 80 per cent of women and about 85 per cent of babies are not immune to whooping cough as demonstrated by lack of protective antibodies. These two statements are based on sound statistical findings which the authors quote.

As an added attraction, they suggest that vaccine and toxoid therapy may serve to suppress formation of anti-Rh antibodies.

A program is presented of combined, active, maternal immunization remedying immunologic deficiencies of the mother to the immunologic advantage of the offspring.

JAMES P. MARR.

Wiener, Alexander S., and Hyman, Malcolm A.: Mistreatment of Congenital Hemolytic Disease (Erythroblastosis Fetalis) by Transfusions of Rh-Positive Blood and Maternal Serum, *J. Pediat.* 29: 498, 1946.

A case is presented which demonstrates the ineffectiveness of Rh-positive blood as compared with Rh-negative blood, and the danger of the use of maternal serum when treating infants with congenital hemolytic disease.

Department of Reviews and Abstracts

Selected Abstracts

Gynecology

Teilum, Gunnar: Gonocytoma. Homolatus Ovarian and Testicular Tumors. I. With Discussion of "Mesonephroma Ovarii," *Acta path. et microbiol. Scandinav.* 23: 242-521, 1946.

Teilum, of the University Institute of Pathological Anatomy at Copenhagen, details exhaustively the morphologic similarity between an ovarian tumor (misinterpreted, according to Teilum, by Schiller in *Am. J. Cancer*, 1939, as mesonephroma) and the more frequently encountered solid or cystic adenopapilliferous tumors of the testis, sometimes teratoid in character. Upon a comparison between tumors of this type to seminoma (dysgerminoma) and the chorioma, the author suggests a group of two homologous tumor series between which his present case report might be considered as an "intermediate" form.

The writer feels that the gonocytomas derive their histogenetic origin from early stages of the germ cells in the testis or from the homologous remnants of the medullary cords in the ovary. In the latter organ, thus not only the dysgerminoma, but also the intermediate form (his gonocytoma II) and the primary chorioma (gonocytoma III) appear as a morphogenetically defined group originating from a particular testicular anlage. The author reports a case of ovarian mesonephroma which he is of the opinion is a true mesonephroma, in contrast to a form described erroneously by Schiller as "mesonephroma ovarii."

The writer concludes that his classification affords a foundation for a more exact histogenetic classification, comprising both ovarian and testicular tumors. C. E. FOLSOME.

Charles, A. H.: A Case of Hydatidiform Mole at Age 52, *Brit. M. J.* 4473: 460, 1946.

The author reports a case of hydatidiform mole occurring in a 52-year-old gravida ii, para i. The patient, who had a Fothergill operation eight years previously, complained of two months' amenorrhea and a brown vaginal discharge of one month's duration. Carcinoma of the body of the uterus was suspected, but an endometrial biopsy revealed a mole. Treatment consisted of a total hysterectomy and bilateral salpingo-oophorectomy.

A brief review of the literature with respect to age incidence of this condition is included, and it is pointed out that hydatidiform mole occurs more frequently between the ages of 20 and 30 years, but the incidence is $2\frac{1}{2}$ times greater in women over 40. Because of the possible subsequent occurrence of chorionepithelioma, he advocates total hysterectomy in women over 40 years of age. R. GORDON DOUGLAS.

O'Connor, Cornelius T., and Bradley, Joseph J.: Retroperitoneal Hemorrhage Complicating Pregnancy, *New England J. Med.* 235: 648, 1946.

The authors present a report of a multipara, who, at the eighth month of gestation, developed a hematoma probably from hemorrhoidal veins, which filled the cul-de-sac of Douglas, and so caused sufficient dystocia to necessitate cesarean section. The hematoma was left undisturbed and eventually absorbed. JAMES P. MARR.

850 cases in which it was possible to examine the blood of both mother and child. They confirmed the already well-recognized importance of the Rh factor in the production of hemolytic disease of the newborn. The writers demonstrated a statistically significant effect of Rh incompatibility in relation to total fetal abnormalities, although the incidence of individual abnormalities such as stillbirth and prematurity was probably too small for valid analysis.

The authors call attention to the evidence that A, B, O incompatibility may be a cause of hemolytic disease, especially the milder manifestations such as late anemia since (1) there was a rise in the iso-agglutinin titer in the maternal serum, and (2) because in 595 cases there was complete compatibility between the maternal and infant blood in which there were only two doubtful cases of *icterus gravis*.

The writers report a higher incidence of *icterus gravis* than in most previously reported series, 10 of 850 cases, an incidence of 1 in 85 as reported; e.g., to 1 in 200 cases by Burnham. There was no correlation found between the anti-Rh titer of the maternal serum and the severity of the hemolytic disease in the infant. The iso-agglutinin titer in the maternal serum, early in pregnancy, was not significantly higher in those cases in which there was a possibility of immunization by the fetus than it was in those in which the mother and child belonged to compatible blood groups. At, or more often shortly after, delivery, the titer of the maternal isoagglutinins corresponding to the infant's A or B factor became elevated. This rise appeared to be associated in most instances with the secretor state in the infant; but in some mothers of the O group, a nonspecific rise of a much lower degree was noted in the antibody not corresponding to the infant's antigen.

Among two series of cases, the one consisting of 100 Rh-positive and 100 Rh-negative women, and the second series of 1,379 women unselected in respect to the Rh factor, there were no significant difference between the total incidence of obstetric accidents in Rh positive and Rh negative. On the other hand, there was among the Rh-negative women a significantly higher incidence of prematurity, stillbirths and *icterus gravis neonatorum*. C. E. FOLSOME.

Robbins, S. L., Parker, F., Jr., and Doyle, W. C.: The Use of the South African Frog (*Xenopus Laevis*) in the Diagnosis of Pregnancy, *New England J. Med.* 234: 784, 1946.

The extrusion of eggs by the South African clawed frog on stimulation by mammalian gonadotropic hormones, such as are excreted in the urine of women during pregnancy, offers a desirable test for pregnancy. Eight to ten hours are required for the reaction.

In a carefully controlled series of 100 consecutive routine urine analyses, the test gave no false-positive reactions, but in four cases of low-titer urines it failed to give a positive reaction. JAMES P. MARR.

Wiener, A. S., and Sonn, Eve B.: Permeability of the Human Placenta to Iso-Antibodies, *J. Lab. & Clin. Med.* 31: 1020-1024, 1946.

The authors describe two cases of erythroblastosis due to A and B sensitization. By means of comparative titrations by the agglutination and conglutination techniques of the alpha and beta antibodies in the maternal and infants' sera the writers found indications that glutinins (univalent antibodies) traversed the placenta more readily than agglutinins (bivalent antibodies). The authors conclude that this evidence supports the hypothesis that glutinins, or blockers, are comprised of smaller molecules than agglutinins. Eleven of fifteen references are those of the senior author. C. E. FOLSOME.

Abortion

Bloch, Suzanne: Abortion in Mice From Injections of Colostrum and Milk, *Gynaecologia* 121: 204-212, 1946.

Bloch, of the Zoological Institute at Basel University, demonstrated that the intraperitoneal injection of cow's colostrum and cow's milk produced abortion in pregnant mice.

Naturally, when the infant's body contains only small amounts of Rh antibodies, the disease is self-limiting, and recovery follows whether Rh-positive or Rh-negative blood is transfused. But the argument to use Rh-positive blood when treating erythroblastosis infants in order to absorb excess antibodies and thus bring about a cure more rapidly is fallacious.

A suggestion that the mother is the ideal donor for all cases of erythroblastosis, including those due to A-B sensitization is important to remember when Rh-negative donors are not available. Two washings of her blood in saline are sufficient to remove the plasma containing the harmful antibody.

JAMES P. MARR.

Swan, Charles, and Tostevin, A. L.: *Congenital Abnormalities in Infants Following Infectious Diseases During Pregnancy, With Special References to Rubella*, M. J. Australia 19: 645, 1946.

The authors report the investigation of 56 infants and two fetuses. Forty-six of them were found to have congenital defects. In 40 instances the mothers suffered from rubella in pregnancy. Thirty-six of the infants and fetuses exhibited congenital defects. Among these cases, four of the mothers had rubella in the first month of pregnancy, 19 in the second month, eight in the third month, two in the fourth month, and one in the fifth, sixth, and eighth months. In the remaining case the duration of the pregnancy at the time of infection was not determined. In three cases in which the infant born subsequently was normal, the mothers had contracted the disease in the second, fourth, and sixth months of pregnancy, respectively. In two instances in which rubella was contracted less than a fortnight before conception, the offspring were apparently normal. The infectious diseases during pregnancy in the remaining 16 cases included eight cases of morbilli (two babies abnormal), three cases of mumps (all babies had defects), two cases of varicella (one baby deformed), two cases of herpes zoster (both babies abnormal), and one case of scarlet fever (baby defective).

WM. BERMAN.

Miller, Herbert C.: *The Effect of Diabetic and Prediabetic Pregnancies on the Fetus and Newborn Infant*, J. Pediat. 29: 455, 1946.

The purpose of this paper is to review our present knowledge of diabetes and to present recent investigations that have been made on the etiology of the high fetal and neonatal mortality in diabetic pregnancies.

The tendency toward an increased birth weight among infants born to diabetic mothers is recognized by all. This has led many investigators to speculate that the growth hormone of the anterior pituitary might be not only diabetogenic for the mother, but growth producing for the fetus.

The high mortality rate of infants born of diabetic mothers has been the object of several studies carried out by White and other workers, and by Smith, Smith, and Hurwitz. The latter conclude from their investigations that there is a deficiency in the production of steroid hormones by the placenta during diabetes which causes fetal death. They have suggested large doses of diethylstilbestrol beginning about the sixteenth week of pregnancy, in order to counteract the lagging production of estrogen which apparently occurs in the latter part of some diabetic pregnancies.

White and Hunt, using estrogen and progesterone, reported marked success in lowering the number of fetal deaths.

The author is of the opinion that it is too early to judge whether or not the replacement therapy employed by the investigators mentioned is going to be uniformly successful in reducing the high mortality among offspring of diabetic mothers.

JAMES P. MARR.

Pregnancy, Physiology, Etc.

Bryce, Lucy, Jakobowicz, Rachel, and McArthur, Norma: *Studies of Maternal and Infantile Blood Factor Relationships*, M. J. Australia 2: 217-224, 1946.

The authors, surveying the data from Queen Victoria Hospital, the Australian Red Cross Transfusion Service, and the Walter and Eliza Hall Institute emerged with a group of

Necrology

CHARLES SUMNER BACON, M.D., identified with medical progress in Chicago for more than half a century, teacher, and author, died at the Grant Hospital there on July 10, 1947, having reached almost his ninety-first year. Graduating from Northwestern University in 1884, he studied abroad for several years, and then served from 1903 to 1926 as head of the Department of Obstetrics and Gynecology at the University of Illinois. He also was associated with the former Lying-in Hospital, and for many years was active in the work of the Municipal Tuberculosis Sanitarium. Dr. Bacon was a member of many medical societies and twice president of the Chicago Gynecological Society. In 1925 he received the Golden Decoration of Honor from the Austrian Republic in recognition of his relief work after the First World War.

Correspondence

To the Editor:

Because of the prevalent opinion that the postcoital examination of the cervical mucus in the sterile patient is a fairly modern diagnostic procedure, I thought it might be of interest to call attention to the following quotation from Sims' *Uterine Surgery* (William Wood & Co., 1873, page 351).

"If we take a drop of semen from the vagina immediately after sexual intercourse, and place it under the microscope, we shall see the hurried movements of seemingly thousands of spermatozoa. But this is not the best way of studying the phenomena of their movements. The best plan is to take a drop of mucus from the canal of a perfectly normal cervix uteri some fifteen or twenty hours after sexual intercourse. We shall then be better able to examine the spermatozoa; for we shall see them in the fluid that serves as the means of their finding their way towards the ovum."

If this test is to be designated by the name of its originator therefore, probably we should call it the "Sims Test," which, I understand, is the title it is designated in England.

C. L. BUXTON, M.D.

NEW YORK, MAY 20, 1947.

Human colostrum, obtained before and after delivery, also caused abortion, but the human milk did not exert this effect. The toxic effect of these agents producing abortion increased with the change from cow or human colostrum to cow's milk, but was not apparent with human milk.

When progesterone was administered simultaneously it was not able to prevent the abortions produced by colostrum and milk injections. The author makes no mention of the content of fat comparison in the cow or human milk.

C. E. FOLSOME.

Anesthesia, Analgesia

Brown, Arthur E.: Spinal Anesthesia and the Pregnant Woman, M. J. Australia 11: 488, 1946.

The author reports a death from spinal anesthesia in a 29-year-old gravida vii who was to have had a cesarean section for a persistent transverse presentation. Her prenatal course had been entirely uneventful. The author reviews the literature on the susceptibility of the pregnant woman to spinal anesthesia.

WILLIAM BERMAN.

Parmley, Ray T., and Adriani, John: Saddle Block Anesthesia—Its Application to Obstetrics, New Orleans M. & S. J. 99: 373, 1947.

Experience with saddle block anesthesia in the management of labor and delivery is described. A wheal is raised with novocaine over the third lumbar interspace and an ordinary spinal needle introduced. Nupercaine, 0.5 c.c. of $\frac{1}{200}$ solution is mixed with 0.5 c.c. of 10 per cent glucose solution in a 2 c.c. syringe. This is injected into the spinal canal while the patient is in a sitting posture. The patient remains in a sitting position for thirty seconds after injection of the mixed solution. Care is taken not to inject at the height of a contraction. The hyperbaric solution being heavier than spinal fluid bathes the sacral segments and produces a sensory anesthesia over the buttocks and vulva area. Motor paralysis also occurs in the perineal muscles.

This anesthesia was used on 156 cases without serious complication. Nausea and vomiting occurred in 10 per cent. A drop in blood pressure averaging 10 mm. of mercury was observed in 50 per cent of the cases. In five cases blood pressure dropped below 80 mm. systolic, but rapidly returned to normal. Anesthesia was established within 2 to 5 minutes and lasted about three hours.

WILLIAM BICKERS.

Mammary Glands

Taylor, Mary D., and Way, Stanley: Penicillin in Treatment of Acute Puerperal Mastitis, Brit. M. J. 4480: 731, 1946.

Ten cases of puerperal mastitis are reported, only one having an abscess. This represented an incidence of one in 154 patients. Penicillin in "large" doses (12,000 to 20,000 units intramuscularly every three hours) was prescribed and nursing encouraged. Disability varied from two to seven days, but pain did not exist beyond three days. The abscess was aspirated on two occasions but was not incised. The authors emphasize the importance of early treatment and the ineffectiveness of penicillin locally.

R. GORDON DOUGLAS.

should serve as a fruitful field for studying early development, rate of growth, and similar aspects of squamous cell carcinoma.

Since July, 1931, 153 patients with leucoplakia of the vulva have been processed through the University of Michigan Hospital. Of these, 143 were seen prior to July, 1945, and were treated in the customary manner with everything from soothing lotions to surgery. These we shall call our *prestudy* group in contradistinction to a *study* group of 36 patients subjected to careful scrutiny and observation since Jan. 1, 1946. This study group includes 25 patients from the prestudy category and 11 new patients first seen during 1946.

The average age for the 143 patients in our prestudy group was 55.6 years. The eldest was 80 and the youngest 23 years. That leucoplakia is not exclusively a disease of the aged is shown by the fact that one of our patients was aged 30 years, and two were 23 years of age. One of the latter was pregnant. Green-Armytage⁵ reported a case of advanced leucoplakia in a pregnant woman aged 42 years. He also mentioned four other instances occurring during pregnancy. Klasten⁶ reported leucoplakia and subsequent kraurosis in a 6-year-old child. The diagnosis was confirmed by biopsy. Ketron and Ellis⁷ noted vulvar changes in an 8-year-old child which they temporarily classified as leucoplakia.

Rigby⁸ states that leucoplakia is uncommon in the Negro race. De Lima Filho¹⁹ listed one Negro woman in his series. There were no Negro patients in our series.

The marriage and parity status among our 143 *prestudy* patients are shown in Tables I and II.

TABLE I. MARITAL STATUS

| | | |
|----------------|-----|--------|
| Married | 97 | 67.7% |
| Widowed | 37 | 25.8% |
| Divorced | 1 | 0.7% |
| Single | 7 | 4.9% |
| Status unknown | 1 | 0.7% |
| | 143 | 100.0% |

TABLE II. PARITY

| | | |
|----------------|-----|-------|
| Parous | 97 | 67.7% |
| Nulliparous | 30 | 20.9% |
| Parity unknown | 16 | 11.1% |
| | 143 | 99.7% |

One hundred fourteen, or 78.5 per cent, of the 143 patients were post menopausal. In 10 the menopause had been artificially induced.

The symptoms complained of are shown in Table III. The average duration of results obtained in the prestudy group.

Thirty-three, or 23.1 per cent, had an associated carcinoma presumably on a leucoplakic basis. This incidence is less than half the commonly cited 50 per cent noted by Taussig.

Treatment for the prestudy group included a variety of empirical therapy and excision or vulvectomy in 54 cases. There were 13 recurrences (24.7 per

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Original Communications

LEUCOPLAKIA OF THE VULVA*

Preliminary Report

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GYNCOLOGISTS, dermatologists and most experienced physicians have long recognized as a clinical entity the vulvar lesion characterized by grayish white patchy thickening, fissuring, edema, and areas of atrophy. Yet, the etiology of this troublesome lesion is unknown, its clinical course is obscure, the histologic picture controversial, and a satisfactory treatment wanting. Indeed, there is not even complete agreement among physicians as to what the condition should be called. Brewer¹ gleaned 18 different names from the literature, none of which has received universal approbation. It may not matter much just what this entity is called, but there should be agreement on a suitable and appropriate term. For a somewhat similar condition occurring in the mouth Schwimmer,⁴ in 1877, coined the word "leucoplakia." Tausig,² in this country, fostered use of this term for the vulvar lesion. Since the condition generally is characterized by an easily visualized grayish white patchy thickening frequently associated with fissuring, edema, and later with atrophy, and, since the disease is by no means confined to postmenopausal women, we prefer the term leucoplakia. In this report the term is used in its broad sense to include both the hypertrophic as well as an atrophic (kraurosis) phase of the disease.

Our interest in leucoplakia stems from two sources: first, an increasing awareness of the numerous shortcomings in our concept of the disease and its treatment. We recognize many of its characteristics, but, like so many pieces of a jigsaw puzzle, we do not know how they all fit together. Second, leucoplakia appears to have considerable cancer potentiality and for this reason

*Presented before the New York Obstetrical Society, Jan. 14, 1947.

NOTE: The Editors accept no responsibility for views and statements of authors as published in their "Original Communications."

histologic appearance of the atrophy so well described by Montgomery, Counsellor, and Craig¹⁰ and best known under the term kraurosis. Since these two conditions not uncommonly occur as associated lesions in the same patient, the possibility of a transitional phase seems logical. Just which direction the transition goes, however, is still a controversial matter. Taussig seemed convinced that the changes generally grouped under the term hypertrophic preceded those of atrophy. Terrhun,⁹ on the other hand, took the contrary view, and with this Brewer¹ appears to agree. Cinberg³ does not recognize kraurosis as a disease entity. The picture is further confused by the trauma from scratching or rubbing, secondary infection, and such conditions as Lichen Planus which presents a histologic picture not unlike that seen in leucoplakia. (Figs. 1 to 9.*) Perhaps as we continue to observe the individual patients in our series and repeatedly biopsy the lesion we may crystallize the true course of events in leucoplakia of the vulva.



Fig. 1.—Hypertrophic leucoplakia. (1). Stratum corneum showing marked hypertrophy (hyperkeratosis). (2). Stratum granulosum showing a marked increase in the normal number of cell layers. Note the increase or capping effect over the rete pegs. (3). Stratum spinosum or prickly cell layer showing marked hyperplasia with elongation and widening of the rete pegs (acanthosis). (4). Stratum germinativum or basal layer showing enlargement of the cells with an increase in their grouping over the tips of the rete pegs. Liquefaction necrosis not yet remarkable. (5). Early cellular infiltration in the dermis.

Since the average age of women with leucoplakia of the vulva is 55 years, it is not surprising that a reasonable number should present other evidence of organic disease. A list of coexisting disease in our study group of 36 patients is shown in Table VI.

Some of the 36 patients had more than one co-existing organic disease. We are not impressed by any apparent relationship to the vulvar lesion. There were no diabetics in our study group.

The blood pressure determinations were not remarkable. Nine patients revealed a pressure of 150/90 or over.

*The tissue sections and photomicrographs were prepared and are presented through the courtesy of the Department of Pathology and Photography of the University of Michigan Hospital.

TABLE III. SYMPTOMS

| | |
|-------------------------------|-----|
| Pruritis | 108 |
| Irritation and burning | 31 |
| Vaginal discharge | 20 |
| Pain and burning on urination | 11 |
| Pruritus ani | 9 |
| Ulcers | 8 |
| Pain in vulva | 8 |
| Bleeding | 6 |
| Dyspareunia | 2 |

TABLE IV. RESULTS OF TREATMENT IN PRESTUDY GROUP

| | | |
|----------------------|-----|-------|
| Unimproved | 21 | 14.6% |
| Moderate improvement | 25 | 17.4% |
| Greatly improved | 26 | 18.1% |
| Died | 16 | 11.1% |
| No follow-up | 55 | 38.3% |
| | 143 | 99.5% |

cent) among the surgically treated patients. Table IV gives a rough evaluation of results obtained in the *prestudy* group.

These results should not be interpreted optimistically. Experience has shown that improvement is frequently temporary. Furthermore, the results shown in Table IV do not reflect the heartache and discomfort suffered by these patients with each succeeding therapeutic failure or as a result of genital contraction following vulvectomy. Neither does it portray the futility felt by the physician in his search for a cause and cure.

Our planned study of leucoplakia began in January, 1946. Since then 36 patients (11 new and 25 return cases) have been processed according to the schedule shown in Table V. For a variety of reasons it was not possible to achieve the full prescribed study for every patient. Such data as were obtained form the basis for the remainder of this report. In developing this program of study it was hoped that we might:

a. Investigate many of the frequently voiced but inadequately studied causative factors. By so doing we hope to clear the way for further study regarding etiology later on. This preliminary report is largely a summation of this phase of our work.

b. Contribute toward a better understanding of the clinical course of leucoplakia.

c. Gain a clearer picture of its histopathology through study of repeat biopsy material.

d. Improve our treatment.

e. Evaluate more accurately its precancerous potentialities.

While our experience with leucoplakia of the vulva has been extensive, it did not become intensive until 1946. We have purposely avoided becoming wedded to any fixed concept of the disease beyond that which has been necessary to serve as a common meeting point for discussion. We recognize the clinical characteristics and the various histologic pictures presented by advanced leucoplakia of the vulva. We are also familiar with the clinical and

TABLE V. LEUCOPLAKIA DATA SHEET

| UNIVERSITY OF MICHIGAN HOSPITAL | | | | | | | |
|---|-------------|-----------|----------------------|--|--|--|--|
| Department of Obstetrics and Gynecology | | | | | | | |
| Name_____ | Age_____ | | Hospital Number_____ | | | | |
| Address _____ | | | | | | | |
| Marital Status_____ | Parity_____ | Race_____ | Series Number_____ | | | | |
| 1. History | | | | | | | |
| 2. Physical examination | | | | | | | |
| 3. Dermatology reference | | | | | | | |
| 4. Allergy reference | | | | | | | |
| 5. Psychiatry reference | | | | | | | |
| 6. Medical reference | | | | | | | |
| 7. Oral surgery reference | | | | | | | |
| 8. Urinalysis | | | | | | | |
| 9. Blood study | | | | | | | |
| 10. Blood ascorbic acid | | | | | | | |
| 11. Blood vitamin A | | | | | | | |
| 12. Gastric analysis | | | | | | | |
| 13. Biopsy | | | | | | | |
| 14. Vaginal smears | | | | | | | |
| 15. 17 Ketosteroids | | | | | | | |
| 16. Estrogen assay | | | | | | | |
| 17. Gonadotropins (F.S.II.) | | | | | | | |
| 18. Culture (bacterial) | | | | | | | |
| 19. Yeast culture | | | | | | | |
| 20. Photograph | | | | | | | |
| 21. _____ | | | | | | | |
| 22. _____ | | | | | | | |

TABLE VI. COEXISTING ORGANIC DISEASE

| | |
|---|---|
| Hypertension | 9 |
| Obesity | 8 |
| Organic heart disease | 5 |
| Arthritis | 5 |
| Secondary anemia | 4 |
| Pernicious anemia | 2 |
| Generalized arteriosclerosis | 2 |
| Pelvic relaxation | 3 |
| Menopausal bleeding | 2 |
| Cervical polyp | 1 |
| Uterine fibroids | 1 |
| Asthma | 1 |
| Varicosities of legs | 1 |
| Tuberculosis (arrested) | 1 |
| Hypothyroidism | 1 |
| Chorioretinitis | 1 |
| Spina bifida occulta | 1 |
| Normal healthy women without associated disease | 7 |
| Pregnancy | 1 |

Blood serology was negative in all but one instance. De Lima¹⁰ considered syphilis a strong predisposing factor.

Urinalyses were negative in all but four patients. One of these was found to have occasional glycosuria, while three others showed evidence of urinary tract infection.

Twenty-four patients had complete blood studies. Of this number 8 (33.3 per cent) were reported as normal by the hematologist. Ten (41.6 per cent) showed evidence of infection as indicated by increased sedimentation rate.



Fig. 2.—Transitional type of leucoplakia (leucokraurosis). (1). The stratum corneum included in this bracket shows parakeratosis (retention of the surface cell nuclei) with some edema and loss of lamination. The granular layer is partially absent in this segment, indicating rapid proliferation of the epidermal cells. (2). The dermis at the right is heavily infiltrated with lymphocytes. (3). Hyperkeratosis of stratum corneum. (4). Moderate acanthosis throughout the stratum spinosum. (5). The dermis at the left reveals a marked collagenous degeneration which extends more than two-thirds across the section. Note the blood vessels in this area have been almost entirely obliterated. (6). Dilated blood vessels at the margins of the areas of active infiltration. (7). The basal layer in this area shows edema and loss of palisading with patchy liquefaction necrosis.

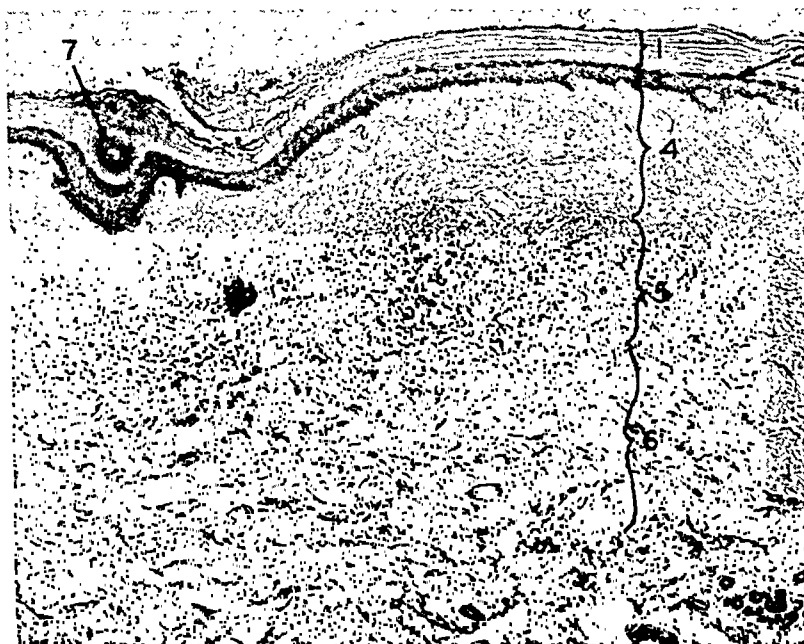


Fig. 3.—Moderately far-advanced atrophic leucoplakia (kraurosis). (1). Hyperkeratotic stratum corneum. (2). The stratum granulosum is easily made out though patchy in areas. (3). The prickly cell layer is atrophic. Practically all evidence of the rete pegs has disappeared, having been compressed by changes in the upper dermis. Note: The basal cell layer is fragmented and irregular having lost the orderly palisade appearance of normal germinal cells. This is due to liquefaction necrosis and intercellular edema. (4). The upper portion of the dermis has undergone hyaline and collagenous degeneration. (5). The mid-dermis shows a moderately diffuse cellular infiltration. (6). The lower dermis shows very little change other than some increase in fibrosis. (7). A keratotic plug in an epidermal orifice.



Fig. 6.—Transitional leucoplakia showing melanin pigment. (1). Along the superficial dermis pigment is seen. Hyaline areas adjacent to these melanin agglutinations probably accounts for its being hyaline. The melanin originated in melanoblasts of the basal cell layer but was liberated by liquefaction necrosis of that layer, and later phagocytized and trapped in the homogenized tissue of the superficial dermis. (2). Stratum corneum shows little or no hyperkeratosis. (3). Focal lymphocytic infiltrations. (4). Dilated apocrine sweat gland. (5). Smooth muscle bundle. (6). Acanthosis with elongation of the rete pegs which are being compressed by the underlying, dermal, hyalin changes. (7). Edema and hyaline, collagenous degeneration in the superficial dermis.

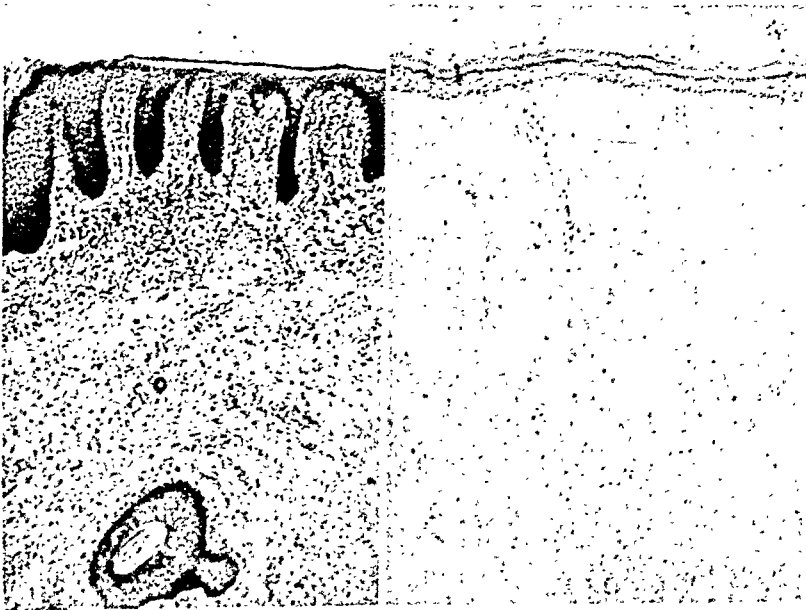


Fig. 7.—Tissue sections taken from a partial vulvectomy. These show a marked contrast from a hypertrophic leucoplakia on the left to a far-advanced atrophic leucoplakia (kraurosis) on the right, occurring simultaneously in the same patient.

toxic granulations, or an increased white count. The fact that 41.6 per cent revealed evidence of infection is interesting in view of the inflammatory infiltration seen in the dermis in leucoplakia. Since 50 per cent of the patients studied showed no evidence of infection in the blood picture it is probably safe to assume that the changes noted were due to infection elsewhere in the body. Two of the 24 patients having complete study demonstrated the picture of pernicious anemia and two revealed idiopathic hypochromic anemia, a

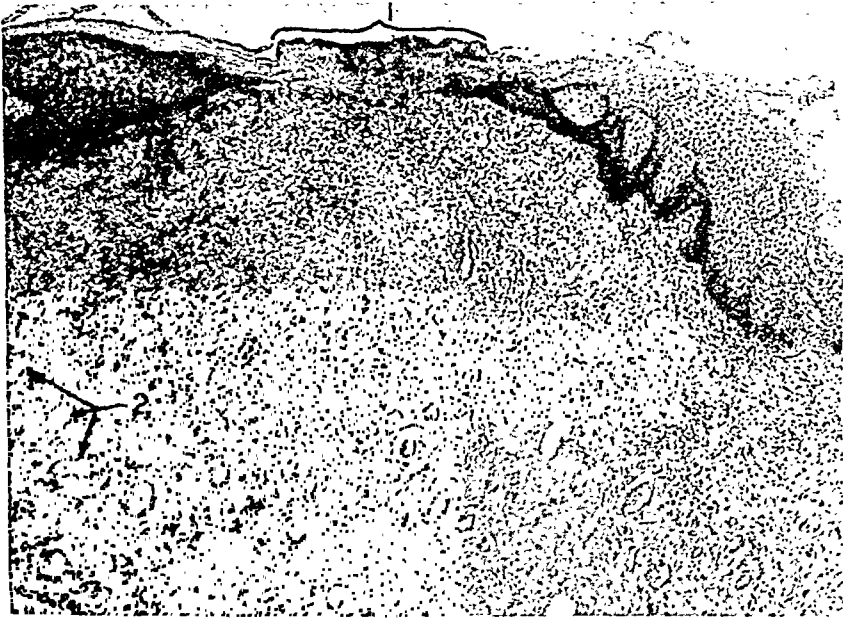


Fig. 4.—Leucoplakia showing fissuring. (1). Area of fissure showing some secondary infection and granulation tissue. There is marked cellular infiltration throughout the section. (2). Numerous dilated vessels of the dermis, part of the granulation tissue.



Fig. 5.—Leucoplakia showing dermal edema and early collagenous change. (1). Only slight hyperkeratosis. (2). There is still evidence of acanthosis. The rete pegs are compressed and show atrophy. (3). The upper dermis shows marked edema which has replaced the cellular infiltration and the blood vessels of the area. (4). Lower dermis showing moderate evidence of cellular infiltration.

higher incidence than we would normally expect. Minor blood abnormalities were noted in two patients.

Study of the vaginal secretions showed only one patient with active trichomonas vaginalis vaginitis.

Yeast cultures were positive in five, but clinical evidence of yeast infection was not evident in any of these five individuals.

Twenty-six of the 36 patients in our study group were examined by a dermatologist. In 21 instances he concurred in the diagnosis of leucoplakia. In three his diagnosis was *Lichen Simplex* or *Lichen Planus*, but two of these had what histologically and gynecologically was considered to be leucoplakia. In two others his diagnosis was neurodermatitis and monilia vulvitis. Both of these patients had the histopathology of leucoplakia.

Because nervousness and emotional instability is frequently noted in patients with pruritis, a careful evaluation of the emotional status was deemed an important part of this study. Consequently, psychiatric consultation was requested and a definite report received for 32 of our study group. The findings are grouped as follows:

TABLE VII. PSYCHIATRIC CONSULTATIONS

| | | |
|---|----|--------|
| Definite contributory psychoneurotic background | 7 | 21.3% |
| Some emotional instability but of questionable significance | 13 | 40.6% |
| No evidence of any psychoneurotic contributing factor | 11 | 34.4% |
| Organic brain disease | 1 | 3.1% |
| | 32 | 99.4 % |

The possibility of a conversion type psychoneurosis predisposing to the development of a chronic irritative vulvar lesion has long been suspected. Emotional instability is likely to be a factor in aggravating and prolonging the pruritic phase of the disease, but we cannot yet assume a cause and effect relationship. Future contributions on this aspect of the disease should be of considerable interest.

Parks¹¹ emphasized the similarity between certain oral and vulvar lesions. Fourteen of our patients were examined by oral surgeons. One revealed two small patches presumably of leucoplakic character and four showed either gingivitis or stomatitis. Chronic irritation is thought to be a factor in leucoplakia of the mouth; and, we have given considerable thought to irritation, such as trauma from rubbing or scratching, as a causative factor in vulvar leucoplakia, but we have not yet been able to evaluate its role as an etiologic factor.

Twenty-five of our group were studied with reference to allergic manifestations. Fourteen, or 56 per cent, had no allergic history or recognizable sensitivity. Eleven, or 44 per cent, revealed an allergic background of variable severity, and in two the pruritis was somewhat relieved after removal of the offending allergen.

Because of the hyperkeratoses noted in vitamin A deficiency the possibility of leucoplakia being a nutritional disease has been of more than casual

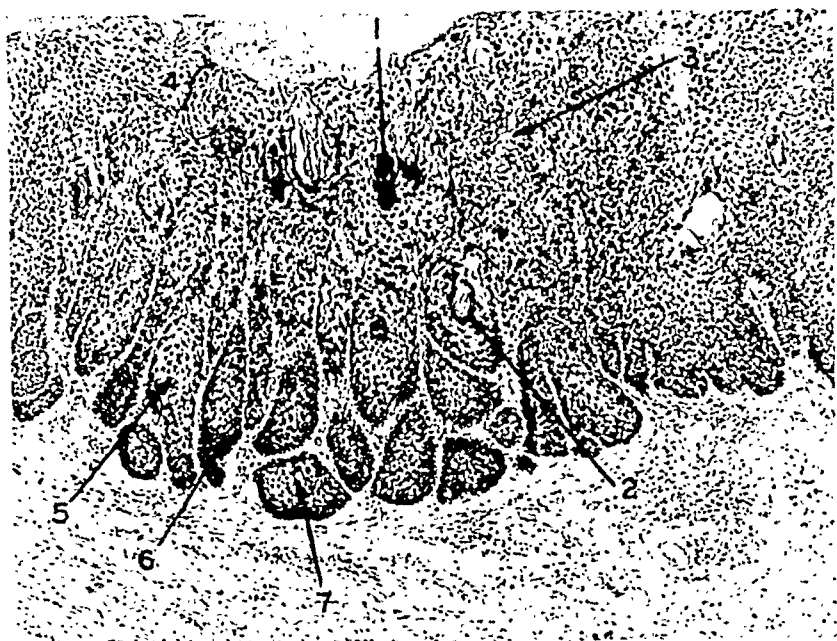


Fig. 8.—Intraepidermoid carcinoma developing in leucoplakia. This type of lesion has all the characteristics of Bowen's disease and must be judged by the same criteria. These are listed: (Lee McCarthy, *Histopathology of Skin Diseases*, St. Louis, 1931, The C. V. Mosby Co., p. 452). (a). Hypertrophic epithelium with dyskeratosis. (Faulty development of the epidermis in which the prickle cells undergo abnormal, premature or imperfect keratinization). (b). Preponderance of intracellular edema over intercellular edema. (c). Numerous mitotic figures. (d). Clumping of large cells with giant nuclei. (e). Hyper- and parakeratosis of the stratum corneum with invagination through the stratum granulosum. (f). General confused appearance of the basal layer.

In reference to Fig. 8: (1). Invagination of the stratum corneum through the stratum granulosum. (2). A keratin plug deep within the prickle cell layer. (3). Area showing marked intracellular edema. (4). Stratum corneum showing marked hyper- and parakeratosis. (5). Prickle cells deep within hyperplastic epithelium and showing loss of polarity, premature keratinization and a tendency to form intraepidermal pearl configurations. (6). Loss of polarity of the basal cell layer. (7). Within this area are few large cells with large nuclei. Mitotic figures cannot be made out at this magnification.

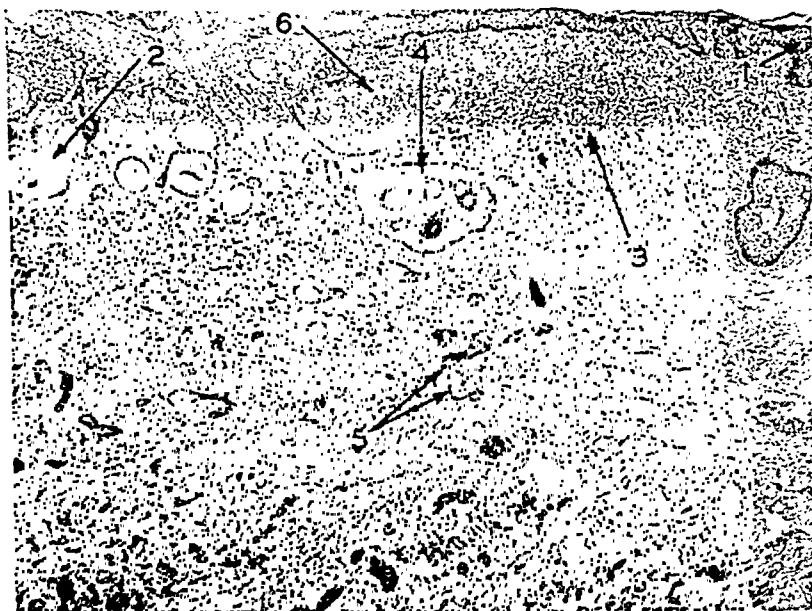


Fig. 9.—Carcinoma developing in an atrophic leucoplakia (kraurosis). (1). Atrophic epithelium showing an atypical arrangement of the cells. (2). Keratohyalin mass below the epithelium surrounded by carcinoma cells. This is a cornifying squamous cell carcinoma. (3). Inflammatory cellular infiltration. (4). Carcinomatous downgrowth with small keratohyalin plugs. (5). Small nests of carcinoma cells. (6). Collagenous tissue of the dermis which is one morphologic feature of atrophic leucoplakia (kraurosis).

Blood plasma ascorbic acid levels were determined for 22 patients. The results are shown in Table X. In 14, or 63.6 per cent, the levels were normal or above. Most of the ascorbic acid determinations were by the titration method of Farmer and Abt¹⁴ employing the indicator 2-6 dichlorophenolindophenol. In a few patients ascorbic acid levels were determined by the colorimetric method of Roe and Kuether.¹⁵

| GASTRIC ANALYSIS | | | | | | | |
|-------------------|---------------|--|--|--------------|-----------------|-----------|------------|
| FREE HCl | 47 5 17 44 50 | | | | 18 | | |
| | 40 | | | | 24 | 37 45 | 16 8 |
| NO FREE HCl | | | | | | | |
| PRE MENOPAUSAL | | | | HYSTERECTOMY | 1-3 YRS. | 4-10 YRS. | 11-20 YRS. |
| | | | | | 20+ YRS. | | |
| | | | | | POST MENOPAUSAL | | |

Table IX.

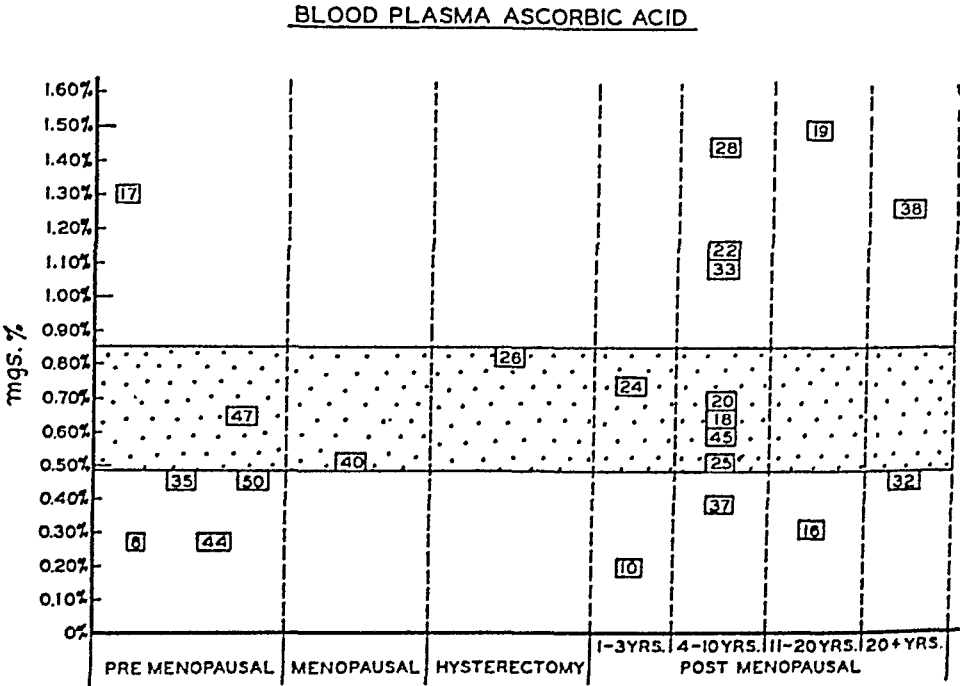


Table X.

The concept that leucoplakia is associated with an estrogen deficiency has been rather widely accepted. Most textbooks on gynecology name estrogen deficiency as an etiologic factor. That this seems unlikely is borne out by our studies and is further supported by the fact that leucoplakia may exist without improvement in young women during pregnancy when the estrogen levels are normally high. Table XI shows the results of urinary estrogen assay on 26 patients in our study group. Twenty-two, or 84 per cent, had normal or above normal estrogen excretion rates. All urinary estrogens were extracted by the method of Gallagher and Koch.¹⁶ The procedure consisting of separate

interest. Swift¹² described a series of patients with vulvar changes which he attributed to vitamin A deficiency. In Swift's opinion the difficulty was not due to an absence of vitamin A but rather, to a lack of hydrochloric acid in the stomach, which he claimed, resulted in failure of utilization of vitamin A. Since pruritus vulvae on a leucoplakic basis is not a particularly common symptom among women with pernicious anemia in whom an achlorhydria is a constant finding this cause and effect relationship does not seem to be borne out in fact. Nevertheless, the possibility of a vitamin A deficiency playing an etiologic role is intriguing. In order to check on this, blood vitamin A determinations were made on 10 patients in our study group and in only one instance was the level below limits accepted as normal (Table VIII). All blood vitamin A determinations were according to the colorimetric method of Dann and Evelyn¹³ using antimony trichloride as the color reagent.

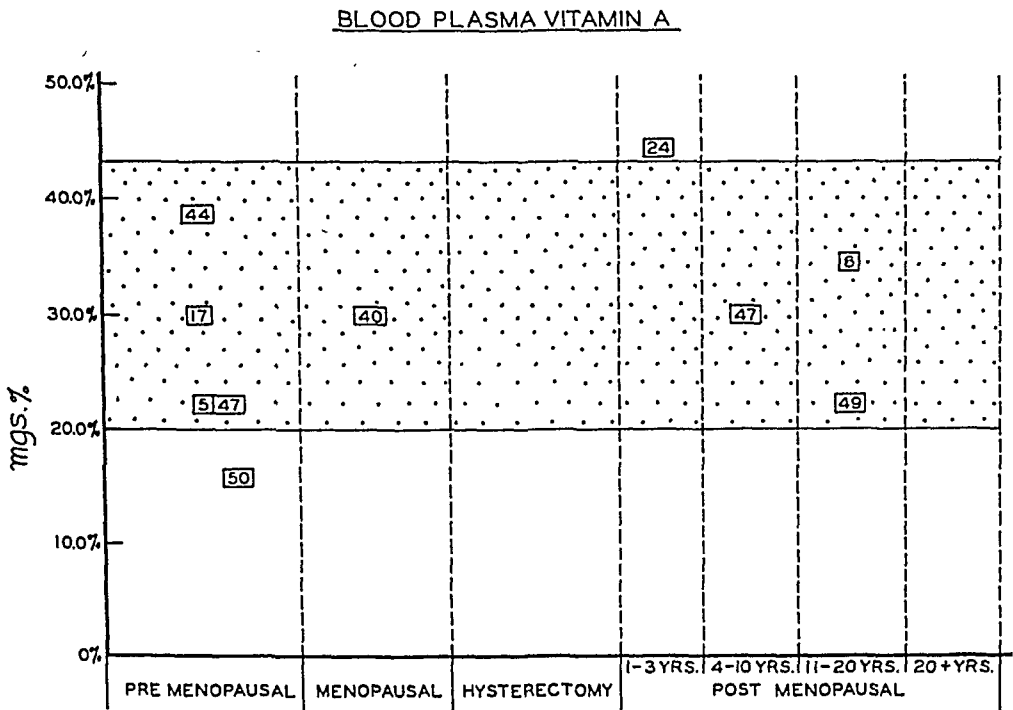


Table VIII.

The gastric acidity was noted in 12 patients. Six revealed free hydrochloric acid and six had no free acid (Table IX). Two of the later were pernicious anemia patients. An achlorhydria is not found in healthy individuals, although it has been stated¹⁸ that 25 per cent of the general population over 65 years of age have no free hydrochloric acid. While the number of acid determinations in our study is not yet large enough to be of significance, the fact that many patients with leucoplakia are elderly, and one-half of the women in our series on whom the test was made did have free hydrochloric acid would seem to minimize any important relationship. Furthermore, three of the six patients with an achlorhydria had a normal or high vitamin A blood level.

In order to explore further the possibility of hormonal imbalance, urinary F.S.H. determinations were carried out on 20 women in our series. The F.S.H. (gonadotropin) test is a biologic test for urinary follicle stimulating hormone, utilizing the uterine response of the immature mouse. The test as used in this study is designed to detect amounts of this hormone in excess of that present in the urine of normal premenopausal women. A positive test is the normal finding for postmenopausal women. A negative test is obtained in premenopausal women except at midcycle when a positive test may be expected. The results revealed in Table XIII show a deviation from normal in three instances (8, 44, 29), but the findings are not sufficiently unusual to be significant.

| | | <u>URINARY (GONADOTROPIN) F.S.H.</u> | | | | | | | | | | | | | |
|----------|----------|--------------------------------------|--|------------|--|--------------|--|-------------|--|--------------|--|-------------|--|--------------|--|
| POSITIVE | NEGATIVE | PRE MENOPAUSAL | | MENOPAUSAL | | HYSTERECTOMY | | 1-3 YRS. | | 4-10 YRS. | | 11-20 YRS. | | 20+ YRS. | |
| | | POST MENOPAUSAL | | | | | | | | | | | | | |
| | | 8 44 | | 23 26 | | 10 24 | | 9 33 37 | | 18 22 25 | | 18 6 19 | | 32 11 38 | |
| | | 35 | | | | | | 29 | | | | | | | |

Table XIII.

Treatment: To our knowledge there is as yet no entirely satisfactory cure for leucoplakia of the vulva. Since its cause is not yet known therapy continues to be largely empirical aimed at the relief of symptoms. To this end innumerable remedies have been advocated, but none has proved entirely satisfactory. During the past year we have tried a number of different preparations, none of which has so far shown any real promise. The remedies being individually tested are:

1. Alfa-Ray ointment applied locally using airtight dressings. Five to 9 treatments at weekly intervals.
2. Ascorbic acid—1,000 mg. daily.
3. Benadryl—50 mg. three times a day orally.
4. Chlorophyll ointment applied locally.
5. Lanolin.
6. Oretone* ointment (5 mg. per c.c.) locally and oreton 10 mg. three times a day orally.
7. Pyribenzamine—50 mg. three times a day orally.
8. Petroleum jelly.

With every item listed subjective improvement has been noted by some individuals but no one remedy has been helpful for all patients. Objective improvement in the appearance of the lesion generally goes hand in hand with subjective relief. None of our 36 study group patients has yet undergone complete recovery. Vulvectomy, partial or complete, had been performed on 54 of our 143 prestudy patients. Thirteen, or 24.7 per cent, had a recurrence

*Generously supplied by Schering Corporation, Bloomfield, N. J.

acid hydrolysis, extraction with benzene, and subsequent separation of estrogens from androgens and 17-ketosteroids with sodium hydroxide. The estrogen fraction was assayed by the biologic method of Allen and Doisy¹⁷ based on the response of the vaginal epithelium of the spayed rat.

Because of the present-day interest in the 17-ketosteroids, these determinations were made on 26 of our study group. The results are shown in Table XII.

URINARY ESTROGEN ASSAY

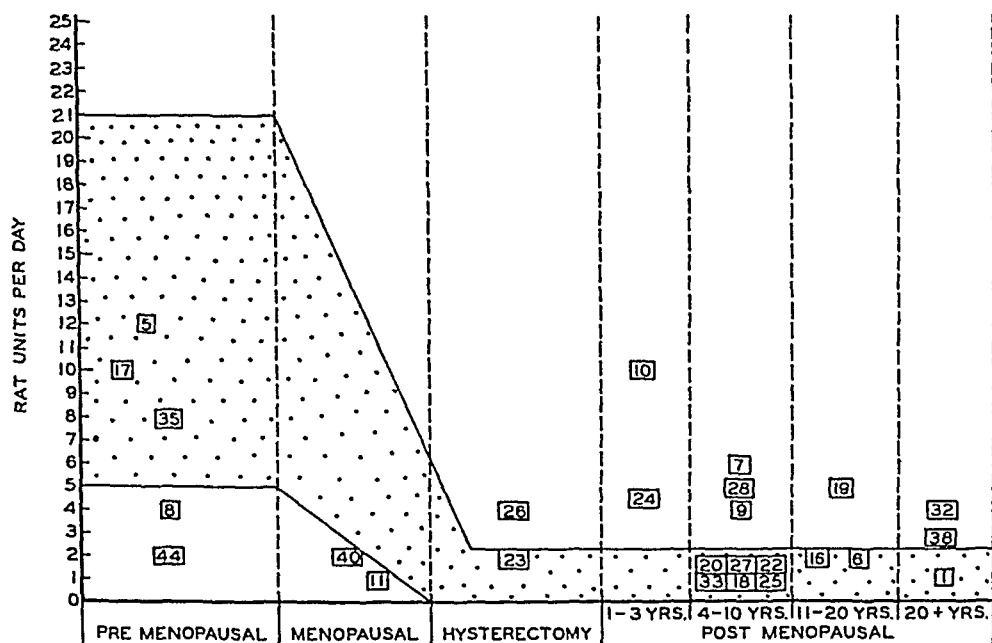


Table XI.

17-KETOSTEROIDS

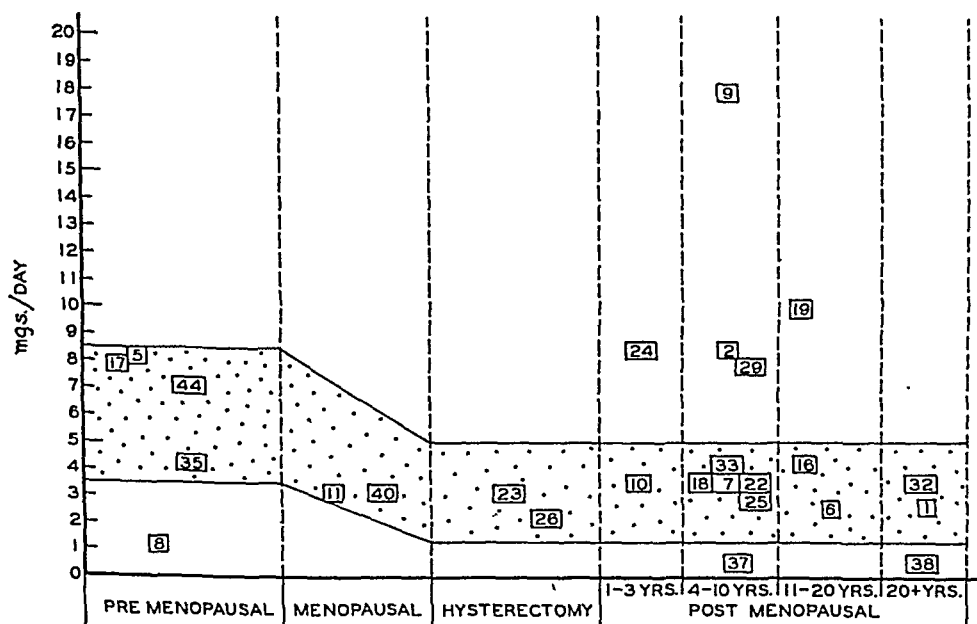


Table XII.

It is strange that we should have this pathologic lesion which in one stage shows hypertrophy and in the next stage atrophy, and it is also rather strange that cancerous development may occur in the atrophic stage of the disease. Looking at the ordinary slides of a case of leucoplakia, one would think that carcinoma would be much more likely to develop in the hypertrophic stage where the plugs are extending down into the dermis.

There is no medical treatment so far that gives permanent relief in a true case of leucoplakia with itching and, later, cracking and fissuring, going on to carcinoma. We have tried all sorts of medicaments at the Sloane Hospital, including estrogenic ointment, stilbestrol ointment, etc., and for a time we thought we were getting results, but the improvement proved to be only temporary.

Analyzing our cases of cancer of the vulva at Sloane Hospital we found that the most common and most prolonged symptom in all cases was pruritus (80 per cent of cases had been preceded by pruritus) and that it lasted over a period of seven or eight years. If these cases of leucoplakia are followed long enough a higher percentage than that mentioned by Dr. Miller will be found to develop carcinoma.

DR. MORTIMER D. SPEISER.—It is my impression that kraurosis and leucoplakia are two separate and distinct clinical and pathologic entities which may occur singly, but are frequently combined. Kraurosis involves the vestibule and is purely an atrophic sclerosis producing a narrowing of the introitus with resulting dyspareunia. Leucoplakia, on the other hand, involves the labia majora, prepuce of the clitoris, the labia minora, as well as the perineal skin. The lesions may be symmetrical or unilateral and asymmetrical.

In so far as the histology is concerned, both entities present different pictures. The kraurosis shows an atrophy of the epidermis, while the fibrous tissue is greatly thickened. In leucoplakia, on the other hand, there are two phases, the hypertrophic, followed by the atrophic. The hypertrophic phase is associated with acanthosis and hyperkeratosis. In the connective tissue below the epithelium are evidences of edema and round cell infiltration. Elastic tissue fibers are notably absent directly below the epidermis. During the atrophic phase hyperkeratosis is still marked, but the other layers show thinning. There is a considerable collagenous deposit replacing the connective tissue directly beneath the epithelium. The elastic tissue is absent up to the layer of the subcutaneous tissue where it seems to be piled up.

The symptomatology in kraurosis is simply dyspareunia unless trauma brings about inflammation and pruritus, whereas in leucoplakia, pruritus is the outstanding symptom, and this is sometimes intractable.

The differential diagnosis of these two conditions is but one phase of the problem, since there are several other conditions which may give rise to whitish areas about the external genitals. Dr. Miller mentioned lichen planus which is characterized by the violet colored papules when it occurs elsewhere on the body, but these lesions take on a whitish appearance when present on mucosal surfaces. Thickened whitish areas known as lichenification may result from long-continued scratching. The pruritus may have its origin in a neurodermatitis, a persistent trichomonad infection, or a chronic eczematous process. Another condition giving whitish areas is lichen sclerosis et atrophicus.

DR. M. N. HYAMS.—Four and one-half years ago I saw two cases of leucoplakia vulvae; diagnosis verified by biopsy and vulvectomy done on both. Subsequently both had severe recurrence of symptoms. One was reoperated upon followed by another recurrence five months later. Then I resorted to vitamin A to combat these symptoms. Since that time eighteen patients with leucoplakia vulvae have been treated with vitamin A. In all cases thorough physical examination, biopsy specimens, and complete laboratory tests were made. Although our series is small, the results have been most encouraging. The blood picture was negative in the eighteen patients, and free hydrochloric acid was absent in 68 per cent. We had two cases of leucoplakia in Negro women. Approximately 250,000 to 500,000 Units of vitamin A were given daily by mouth supplemented by intramuscular injections of 50,000 units twice a week. In addition, all patients received fifteen minims of dilute hydrochloric acid three times daily. Marked relief of symptoms followed

of the disease, and 9 of these are included in our present study group. We have not resorted to surgery in any of our 36 study group patients. For this there are two reasons, thus:

1. Operation has not yet been deemed necessary.

2. We do not share the optimism of many writers on the subject concerning vulvar excision since resection of the involved areas is not infrequently followed by a recurrence, and complete vulvectomy with its subsequent contraction, may result in what amounts to little less than mutilation. While this may not be important in elderly females it is a serious objection to surgical excision in young or middle-aged women. Furthermore, except for patients who develop a recurrence, once the lesion has been excised, opportunity for evaluating its clinical course and responsiveness to medical treatment ceases. Perhaps we shall resort to surgical excision in some of our study group patients in order to achieve symptomatic relief but for the time being we look upon vulvectomy as an imperfect substitute for a medical cure which we hope some day will be available.

Surgery does have a very real place, however, in the management of malignancy of the vulva and for patients with proved carcinomatous change whether on a leucoplakic basis or not, we strongly advocate radical excision including inguinal lymphadenectomy.

For his interest in humanity and generosity in making this study possible, we desire to express our thanks to W. D. Cochran.

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Discussion

DR. BENJAMIN P. WATSON.—My conception of kraurosis was that it was a condition of the vestibule and of the inner aspect of the labia minora and of the vaginal introitus itself, a sclerosing condition causing not itching but pain, which was the prominent symptom (dyspareunia), and that it went on to a very real contraction of the vulvar orifice and of the tissues around the urethra; whereas leucoplakia was external to the vestibule, confined to the labia majora, and never invaded the vestibule itself.

in which the cancer is actually present, but nonsymptomatic. In many cases of so-called leucoplakia or kraurosis vulvae cancer exists histologically.

The time to cure cancer of the vulva is before you know it is cancer and the patient should, therefore, be treated by vulvectomy. The coincidental lesion going down from the vulva across the perineum, then down to the perianal region also needs surgical treatment.

Many cases of perianal leucoplakia with deep creases and folds in the skin of the perianal area can be cured at the same time as the vulvectomy.

The gynecologist should certainly be able to do a vulvectomy for leucoplakia of the vulva or kraurosis vulvae and retain normal function.

DR. FRANK R. SMITH.—The incidence at the Memorial Hospital of cancer of the vulva in Negro women preceded by leucoplakia is about the same as the cross-section of the clinic.

The low incidence of arteriosclerotic women with cancer of the vulva is surprising.

Because of the probability of subsequent carcinoma, the treatment is surgical. Forty per cent of patients coming to Memorial Hospital with cancer of the vulva had prior medical therapy for leucoplakia and pruritus—injections, estrogenic applications, etc.

Women who suffer from pruritus are ripe subjects for psychoneurosis unless given relief, and therefore the factor of psychoneurosis may be effect rather than cause.

DR. HOWARD C. TAYLOR, JR.—We have theorized a lot about constitutional causes for leucoplakia of the vulva, but we must remember that there is also the matter of local tissue predisposition. The disease occurs in circumscribed areas, characteristically on the inner sides of the labia.

Now it may occur here for one of two reasons, either because of a congenital intrinsic peculiarity of the vulval skin, or else because of the geographical position of the skin which brings surfaces in contact in that area.

The second possibility is proved by the fact that when you do a complete vulvectomy and bring in nonspecific skin to the introitus of the vagina you later get development of leucoplakia fairly frequently in the nongenital skin which you have brought in to the vulval region. From this often repeated cervical experiment it appears that the local factor is to be found in the superficial geographical conditions incidental to the apposition of the two layers of skin at the introitus of the vagina and not to any congenital peculiarity of skin associated with the genital tract.

DR. MILLER (Closing).—This report represents an attempt to evaluate some of the theories, and there have been a great many of them, concerning the cause of leucoplakia. It is also an attempt to learn something about the clinical course of leucoplakia. We have taken some of the theories and analyzed them and presented certain data bearing on these theoretical causes, but of course much work remains to be done.

this treatment in the average case. Repeated biopsy specimens showed a decided improvement in the tissues. Approximately fourteen of our patients are relieved at the present time, while the other four were total failures. Of these, two were diabetics, one was syphilitic, and the other had extensive cardiovascular disease. Apparently vitamin A therapy in the presence of severe systemic disease is useless. We hope to report our findings in the near future on 38 additional patients. We believe that with extensive vulval involvement there is a possibility of carcinoma occurring, and these cases should be operated upon. We agree that vulvectomy is not indicated in all patients with leucoplakia vulvae. Following the routine described above, the tissues take on a normal appearance, become moistened, fissures disappear, and the normal folds can again be seen. Microscopic examination showed changes of the tissues to normal. The use of vitamin A in leucoplakia vulvae, from our experience, has a definite place in its treatment.

DR. JOSHUA W. DAVIES.—I would like to mention a patient with leucoplakia who was followed for six years. This patient was bothered considerably with itching, burning and was unable to sleep. She visited various clinics; finally, after about five years, I saw her again. I was alarmed at the extensive degeneration and atrophy of the vulva. Thinking that because of the danger of malignancy she should be subjected to operation, she disappeared from our service. She turned up six months later. At that time both labia were normal and there were no fissures. I assumed that because of improved mental reaction the local area received better nutrition and that accounted for the improvement. However, she returned subsequently with her original complaints with edema, fissures, and swelling around the anus. This makes me think perhaps there is a local tissue resistance which is important in this condition.

DR. MORRIS A. GOLDBERGER.—In 1933 I reported 13 cases of kraurosis vulvae. There was much confusion at that time as to the differentiation between kraurosis and leucoplakia of the vulva. I called all my cases kraurosis vulvae. In this group there were two cases of unsuspected carcinoma. In another group of 13 cases of carcinoma of the vulva, there was coexisting kraurosis in seven.

Since then we have had 34 cases on our service at Mt. Sinai Hospital. Thirteen were diagnosed as leucoplakia vulvae on biopsy. There were five cases of leucoplakic vulvitis without kraurosis. Another 5 had both leucoplakia and kraurosis. In five cases carcinoma was found. In one of those it was grossly evident. In two cases it was unsuspected. Of these five cases, three had kraurosis and carcinoma, and two were leucoplakic with carcinoma.

Vulvectomy was done in 19 of the 34 patients with a little better than 75 per cent follow-up. The follow-up period ranged from three months to seven years.

We have gone through the period of estrogenic hormone therapy with no permanent improvement in the local condition.

We have also tried tattooing in a number of cases but the improvement was only temporary.

We have also tried large doses of vitamin B with varying results.

We are more inclined at our Hospital to divide this condition into two different categories, namely, kraurosis vulvae and leucoplakic vulvitis.

The age groups in the last thirty-four cases that we had were as follows: two were 32 years of age (menstruating women); ten were in the fourth decade of life; and the remaining twenty-two were in the fifth, sixth, and seventh decades of life.

DR. WILLIAM P. HEALY.—The gynecologist is obligated to give the patient the relief to which she is entitled, and that can be done by surgery. Recurrences can also be removed surgically.

I am very radical in my attitude toward this vulvar lesion where the patient shows evidence of damage from itching, scratching, and irritation, thickening of the tissues, hypertrophy, fissures, creases, and raw areas, because I never saw a case of epithelioma of the vulva at Memorial Hospital without a history of this supposedly nonmalignant lesion leucoplakia. There is a very long period of silence, or lack of symptoms, in cancer,

Pathologic diagnosis: Normal uterus.

Corpus luteum: The dimensions before fixation were 1.2 by 0.8 by 0.8 cm. The wall was thin. The granulosa lutein cells in many regions stained well, had intact, well-stained nuclei, and resembled functioning cells (Fig. 1). There were some shrunken cells with pyknotic nuclei scattered throughout the layer. In one local region cell degeneration was markedly advanced. (Fig. 5, AM. J. OBST. & GYNEC. 44: 6, 1942.) The ingrowth of connective tissue was considerable. The central border was composed of a thick layer of well-organized connective tissue. In the granulosa lutein layer the vessels were collapsed and contained no blood. The theca lutein cells were abundantly distributed about the entire periphery and their nuclei were intact.

Endometrium: The endometrium was as thick as 0.45 cm. prior to fixation. The glands were secretory in character, were squashed, and the lumens contained secretion. Involution had occurred. (Fig. 6, AM. J. OBST. & GYNEC. 44: 6, 1942.) There were a few scattered lymphocytes superficially. There was no extravasation of blood. The spiral arteries reached to the surface epithelium.

SPECIMEN 149.—Day 30 of cycle, aged 36 years, para ii, gravida ii. Menstrual history: Onset at age 16 years, 28-day cycle, three to four days' flow.

Pathologic Diagnosis: Uterine prolapse.

Corpus luteum: The dimensions before fixation were 2.5 by 2.0 by 1.2 cm. The wall was thin and wavy. The granulosa lutein cells were shrunken, vacuolated, and in many the nuclei were pyknotic. (Fig. 7, AM. J. OBST. & GYNEC. 44: 7, 1942.) The cells in all regions of the granulosa lutein layer had a similar degree of degeneration. The ingrowth of connective tissue was marked. The central border was composed of a dense layer of connective tissue. The vessels were collapsed, contained no blood, and were surrounded by a thick layer of connective tissue. The theca lutein cells were sparse and were located principally in the angles of the folds of the granulosa lutein layer.

Endometrium: The endometrium was as thick as 0.5 cm. prior to fixation. The squashed glands showed characteristic secretory activity. Involution had occurred. There was an infiltration of leucocytes and lymphocytes superficially. (Fig. 8, AM. J. OBST. & GYNEC. 44: 7, 1942.) There was some extravasation of blood just beneath the surface epithelium. In this region some of the cells of the surface epithelium had pyknotic nuclei. The spiral arteries reached to the surface.

SPECIMEN 221.—Day 28 of cycle, aged 34 years, para ii, gravida ii. Menstrual history: Onset at age 13 years, 28-day cycle, 5 days' flow.

Pathologic diagnosis: Small myoma and residues of pelvic infection.

Corpus luteum: The dimensions before fixation were 2.5 by 1.5 by 1 cm. The granulosa lutein layer is arranged in the usual folds, and some portions are thinner than others. In some regions the granulosa lutein cells are shrunken, in others there are frequent cells with pyknotic nuclei, and in others the cells are large, even, and show little evidence of regression. The central border consists of a thick dense layer of connective tissue. The blood vessels in the granulosa lutein layer are straight, narrow, and contain no blood cells. About the vessels the connective tissue is abundant.

The theca cells are arranged in the angles of the folds, have round plump nuclei and vacuolated cytoplasm.

Endometrium: The endometrium in the fixed and stained preparation is 4 mm. thick. The glands are typically secretory. Involution has occurred. There is marked infiltration of leucocytes and lymphocytes and a moderate extravasation of red blood cells superficially. There are occasional local collections of red blood cells immediately beneath the surface epithelium. A

STUDIES ON THE HUMAN CORPUS LUTEUM*†

Histologic Variations in Corpora Lutea and in Corpus Luteum. Endometrial Relationships at the Onset of Normal Menstruation

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IT IS rather generally accepted that the life cycle of the human corpus luteum, the cycle of the endometrium, and the relationships of these two tissues one to another are constant and are not subject to variations. During their active normal functioning state we believe that this is usually true. Variability does occur, however, in these two tissues and in their relationships during the regressive stage, principally near and just after the onset of menstruation each month.

It is the purpose of this presentation to demonstrate the normal variations and to discuss their clinical importance. Endometrial studies are frequently made in an effort first to determine the presence or absence of a corpus luteum, second, to estimate the functional capacity of the corpus luteum in preparing the endometrium for pregnancy, and third, to study corpus luteum activity in relation to abnormalities of the menstrual cycle. Without proper evaluation of the normal variations these clinical studies may be subject to misinterpretation.

Material

The tissues for this study consist of the uterus with the endometrium and the corpus luteum in each instance. The specimens were obtained from patients who had completely normal menstrual cycles. The ages of the patients varied from 23 to 47 years. Seven of the patients had fibroids and/or residues of pelvic infection. One of the patients had uterine prolapse of a normal uterus, one had a retrodisplaced normal uterus, and one had a normal uterus. Although pathologic lesions were present there had been no alteration of the menstrual cycles from the normal. The menstrual histories were carefully checked during the patient's hospital stay.

The tissues were obtained as surgical specimens. These were studied grossly and then placed in various fixing solutions within five minutes after the blood supply was clamped. The multiple blocks of endometrium were chosen from regions where the endometrium did not overlie a fibroid. This was done to avoid mechanical distortion of the tissue.

Three specimens obtained prior to the onset of menstruation were selected as representative of this period. Seven specimens removed from patients on day 1 of menstruation are reported.

SPECIMEN 255.—Day 27 of cycle, aged 35 years, para vi, gravida vi; menstrual history: Onset at 14 years of age, 26- to 35-day cycles, five days' flow.

*Presented at the joint meeting of the Chicago, Kansas City, and St. Louis Gynecological Societies, Kansas City, Mo., on April 12, 1947.

†Aided by the C. V. Essroger Research Fund and a grant from the Billings Medical Club, Chicago.

Pathologic diagnosis: Small uterine myomas.

Corpus luteum: The dimensions before fixation were 2 by 0.9 by 0.8 cm. The granulosa lutein cells throughout the entire corpus luteum were uniformly degenerated (Fig. 2). The cells were small, irregular in shape, had clear cytoplasm and pyknotic nuclei. In no region were there intact granulosa lutein cells. There was an abundant ingrowth of connective tissue throughout this layer, but the connective tissue border along the central cavity was scant, was not organized, and was consistent with that of a much younger corpus luteum. The blood vessels were narrow, empty, and were surrounded by considerable connective tissue.

The theca interna cells were smaller than the granulosa lutein cells, had vacuolated cytoplasm, and many had irregular, pyknotic nuclei.



Fig. 3.—The endometrium of Specimen 325 has local regions of desquamation. Previous secretory activity of the gland cells is indicated by the abundant secretion in the gland lumens. The corpus luteum of this specimen is shown in Fig. 2.

Endometrium: The endometrium in the fixed and stained preparation was as thick as 0.5 cm. The glands were secretory in type. The spiral arteries reached to the surface. Involution had occurred. Throughout the superficial zone there was an extensive infiltration of leucocytes and lymphocytes, extravasation of red blood cells, and a loosening up of the stromal cells. Sub-epithelial hematomas were frequent. In places the surface epithelium was detached from the underlying stroma. In several small microscopic regions there was desquamation of the superficial endometrium (Fig. 3).

SPECIMEN 303.—Day 1 of cycle. Began to menstruate eighteen hours prior to operation. Age 23 years, para i, gravida i. Menstrual history: Onset at 12 years of age, 28-day cycle, two to seven days' flow.

Pathologic diagnosis: Residues of pelvic infection.

Corpus luteum: The diameter prior to fixation was 2.0 cm. The granulosa lutein cells have little evidence of degeneration (Fig. 4). Many of the cells are still large and the nuclei are round or oval and stain well. Shrinkage in

characteristic loosening up of the stromal cells in the superficial zone has occurred. The spiral arteries reach to the surface.

SPECIMEN 325.—Day 1 of cycle. Patient began to menstruate three hours prior to operation. Age 29 years, para i, gravida i. Menstrual history: Onset at 12 years of age, 24-day cycle, five days' flow.

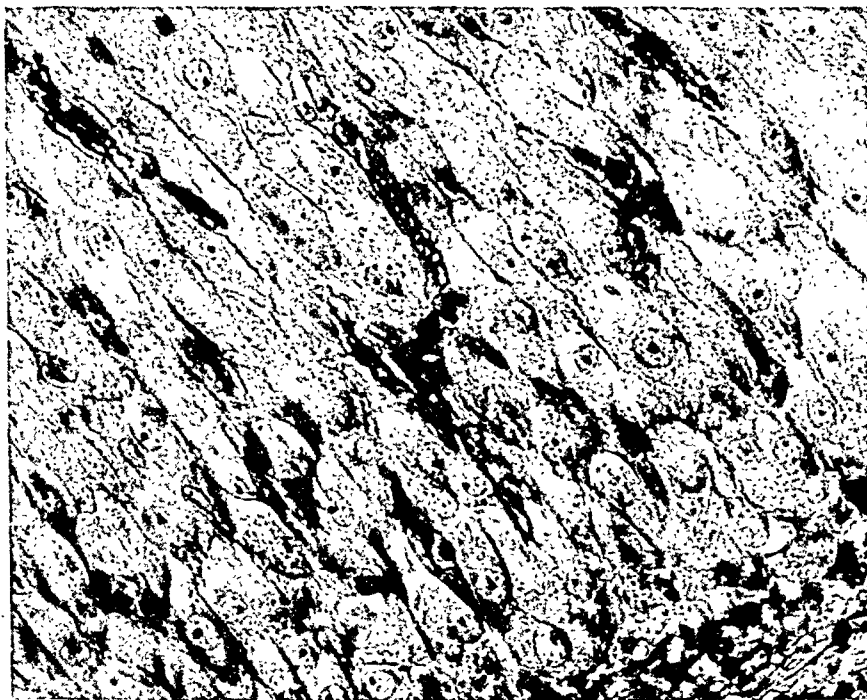


Fig. 1.—Specimen 255. In this portion of the corpus luteum the granulosa lutein cells stain well, are intact, and resemble functioning cells. (Photomicrographs of degenerating cell regions and the endometrium of this specimen are shown in Figs. 5 and 6, *Am. J. Obst. & Gynec.* Vol. 44: 6, 1942.)

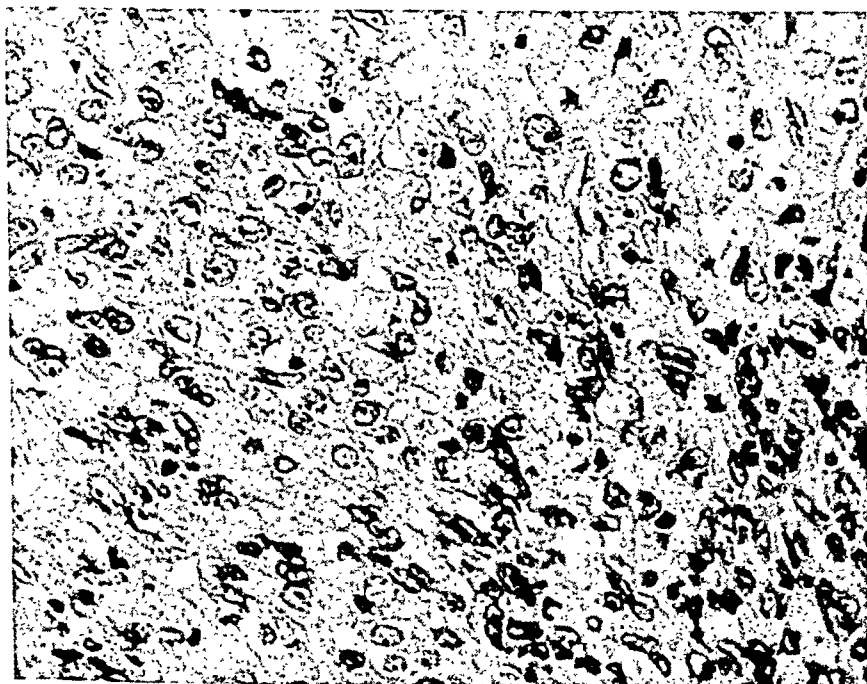


Fig. 2.—The granulosa lutein cells are uniformly involved in an advanced degree of degeneration. (Specimen 325; first day of menstruation.)

some cells has occurred but it is not great. There is little vacuolization of these cells and only a few cells have pyknotic nuclei. Some of the blood vessels in this layer still contain red blood cells. Most, however, are empty. The vessels have rather thick connective tissue borders. The ingrowth of connective tissue is abundant, and the border about the central cavity is thick and well organized.

The theca interna cells are abundant. There is no evidence of pyknosis.

Endometrium: The endometrium in the fixed and stained preparation is 0.3 cm. thick. The secretory glands are squashed and the edema has disappeared from the stroma. The spiral arteries reach to the surface. Involution has occurred. Throughout the superficial zone there is an extensive infiltration of leucocytes and lymphocytes, extravasation of red blood cells, and a loosening of the stromal cells (Fig. 5). In some regions desquamation has occurred but loss of tissue is scant.

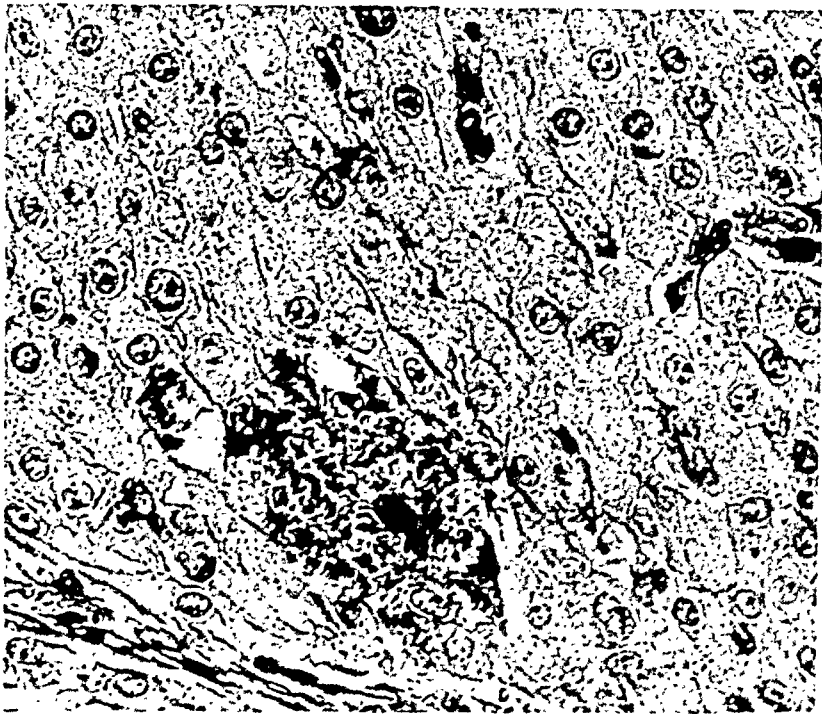


Fig. 6.—The granulosa lutein cells throughout the entire layer evidence slight regression only by a slight reduction in cell size. The cell shapes, staining qualities, and nuclei are similar to those of the physiologic active gland cells. (Specimen 106; first day of menstruation.)

SPECIMEN 106.—Day 1 of cycle. Began to menstruate one hour prior to operation. Age 41, para iii, gravida iii. Menstrual history: Onset at age 11 years, 28-day cycle, seven to eight days' flow.

Pathologic diagnosis: Uterine myoma and residues of pelvic infection.

Corpus luteum: The diameter before fixation was 1.5 cm. The granulosa lutein cells were intact and resembled functioning cells (Fig. 6). Some still remained large, but most were reduced in size. Occasional nuclei were pyknotic. Most, however, stained well and were round or oval. Degenerative changes were minimal. The cytoplasm stained evenly. The blood vessels throughout the granulosa lutein layer were narrow and collapsed. Some contained red blood cells. The ingrowth of connective tissue was moderate. The central cavity had a well-organized connective tissue border.

The theca interna cells were numerous, were smaller than the granulosa lutein cells, had vacuolated cytoplasm, and some of the nuclei stained poorly and had irregular shapes.

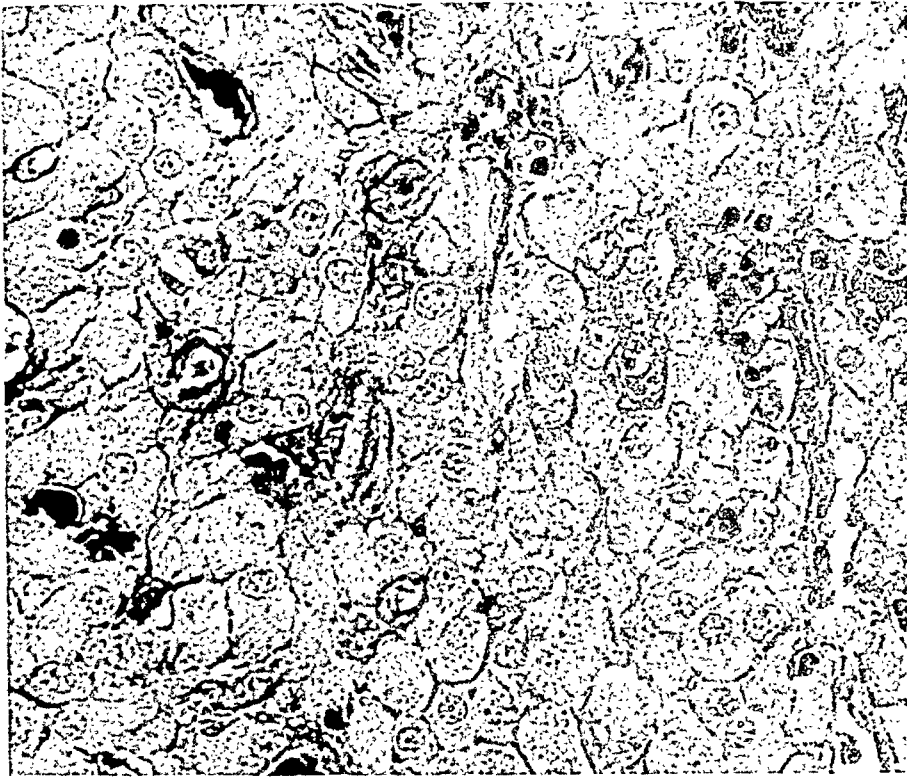


Fig. 4.—The granulosa lutein cells shown in this photomicrograph of Specimen 303 (first day of menstruation) are typical of all cells throughout the granulosa lutein layer. The cells are intact, are only slightly reduced in size, and have little evidence of degeneration. Some blood is still present in the vessels in the granulosa lutein layer.



Fig. 5.—The findings in the endometrium indicate impending menstruation and in some small regions desquamation has occurred. Histologic evidence of some continued corpus luteum secretory activity is shown. (Specimen 303.)

Endometrium: The endometrium in the fixed and stained preparation varied from 0.2 to 0.5 cm. in thickness. Desquamation of the endometrium was extensive (Fig. 7). In no sections was the surface epithelium present. Glands and spiral arteries jutted above the very irregular surface. The glands had evidence of antecedent secretory activity as determined by secretion in the lumens. The cells themselves in some glands had no evidence of secretory activity.

SPECIMEN 224.—Day 1 of cycle. Began to menstruate two hours prior to operation. Age 37 years, para i, gravida i. Menstrual history: Onset at the age of 14 years, 28-day cycle, three to five days' flow.

Pathologic diagnosis: Uterine myomas.



Fig. 9.—In other regions of the corpus luteum shown in Fig. 8, the granulosa lutein cells remain intact and evidence regression only by reduction in cell size.

Corpus luteum: The dimensions of the corpus luteum before fixation were 1.0 by 0.8 by 0.5 cm. Throughout most regions of the granulosa lutein layer the cells were shrunken and vacuolated (Fig. 8). Some had small nuclei and in many the nuclei were pyknotic. In other regions the cells were large, the cytoplasm stained evenly, the nuclei were large, round or oval, and there was little evidence of degeneration (Fig. 9). There was marked infolding of the entire layer. The blood vessels in the layer were narrow, straight, collapsed, and contained no blood. There was a moderate ingrowth of connective tissue. The connective tissue border about the central cavity was not very dense or thick. The centrum contained a large amount of blood.

The theca interna cells were smaller than the granulosa lutein cells, were highly vacuolated, and many had pyknotic nuclei.

Endometrium: The thickest portion of the endometrium in the fixed and stained preparation was 0.25 cm. The endometrial surface was irregular, and considerable desquamation of tissue had occurred (Fig. 10). The glands evidenced still some slight secretory activity in some regions, while in others the

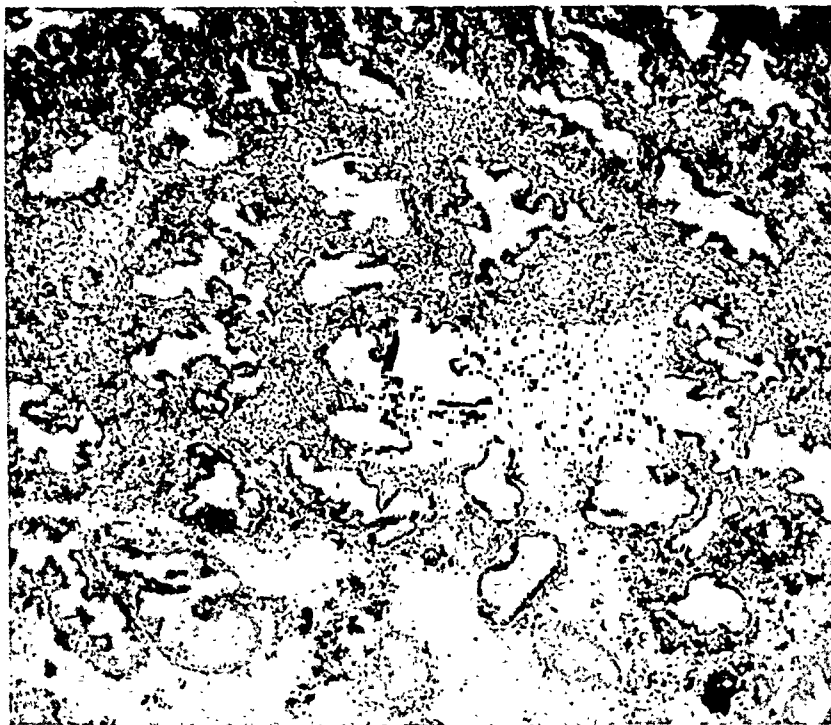


Fig. 7.—The endometrium (Specimen 106) has undergone more desquamation than usual for a specimen removed within one hour after the onset of menstruation. The evidence of antecedent stimulation is less than that in Specimen 303, Fig. 5. The corpus luteum is shown in Fig. 6.

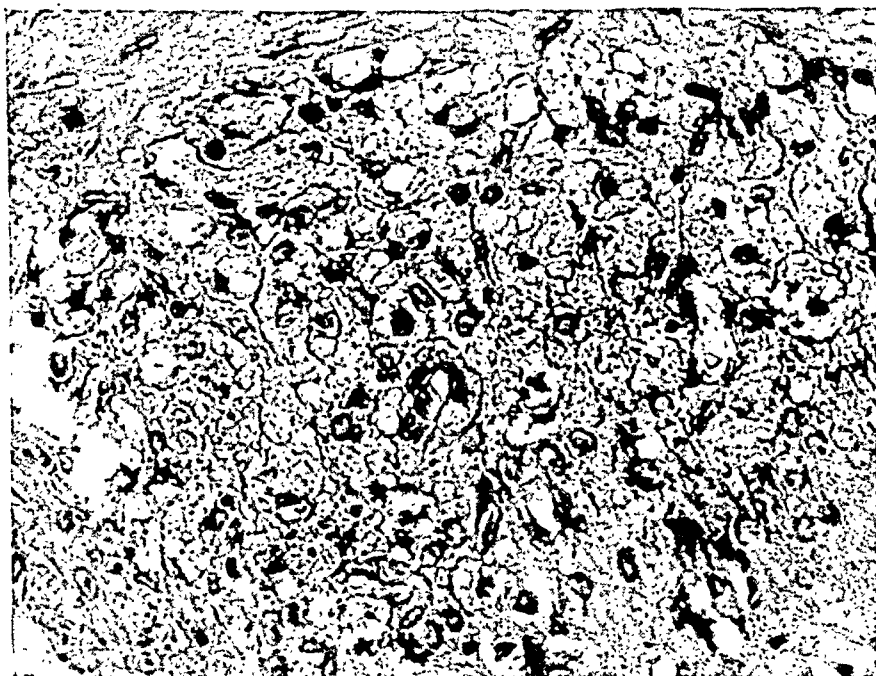


Fig. 8.—This photomicrograph of a portion of the corpus luteum (Specimen 224; first day of menstruation) shows the granulosa lutein cells in an advanced degree of degeneration which is similar to Specimen 325, Fig. 2.

granulosa lutein cells were only reduced in size and had moderate vacuolization. The nuclei and nucleoli remained intact and appeared normal. Pyknosis was not prominent. In some small local regions the granulosa lutein cells had degenerated more and had nuclear pyknosis, irregular sizes and shapes, and clear cytoplasm. The connective tissue was abundant and had extended through the layer, and was organized as a thick border around the central cavity. The central cavity contained a small amount of blood.

The theca cells were small, vacuolated, and had round intact nuclei.

Endometrium: The greatest thickness was 0.2 cm. The surface was irregular, and the surface epithelium was lost in all but a few regions. Desquamation, while general throughout the endometrium, was only moderate, since the regions still covered with epithelium were approximately as thick as those undergoing slough. Some of the glands showed slight to moderate secretory characteristics. In some regions the glands were straight, and demonstrated little antecedent secretory activity.

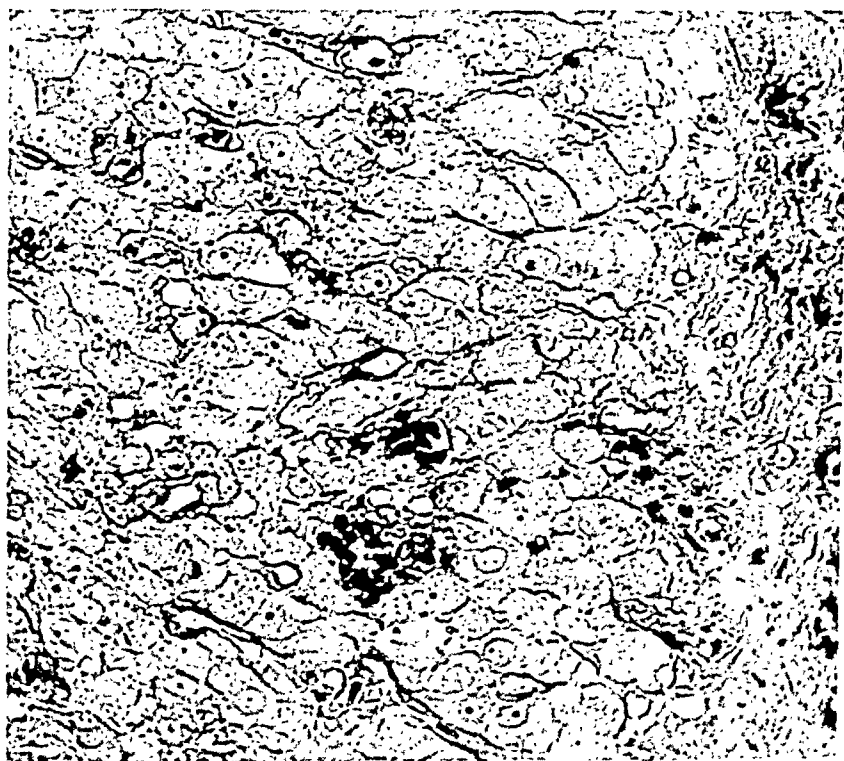


Fig. 11.—Many of the granulosa lutein cells (Specimen 13; first day of menstruation) have evidence of degeneration. Many are only reduced in size and some remain large, stain well, and have round large well-stained nuclei.

SPECIMEN 13.—Day 1 of cycle. Began to menstruate three hours prior to operation. Age 47 years, para iii, gravida viii. Menstrual history: Onset at 14 years of age, 28-day cycle, six to seven days' flow.

Pathologic diagnosis: Uterine myoma.

Corpus luteum: The stigma point was readily identified. The granulosa lutein layer (Fig. 11) was thin and only moderately wavy. The cells were, for the most part small, irregular in shape, many were vacuolated, and pyknosis was common. In some regions, however, the cells were plump, had even stained cytoplasm and normal round or oval nuclei. The blood vessels were narrow and a few contained some blood. There was a moderate ingrowth of connective tissue. The connective tissue border about the central cavity was thick and well organized. There was a slight amount of blood in the central cavity.

The theca cells had the usual vacuolization, and some had pyknotic nuclei.

glands were not secretory in character, but their lumens contained secretion as evidence of their antecedent activity.

SPECIMEN 66.—Day 1 of cycle. Began to menstruate one hour before operation. Age 24 years, para i, gravida i. Menstrual history: Onset at the age of 13 years, 28-day cycle, four to five days' flow.

Pathologic diagnosis: Normal uterus.

Corpus luteum: The dimensions before fixation were 1.8 by 1.2 by 1.0 cm. Degenerative changes involve the granulosa lutein cells rather uniformly throughout the granulosa lutein layer. The cells were shrunk, irregular in size and shape, vacuolated, and many contained pyknotic nuclei. The blood vessels throughout the layer were narrow and contained no blood. The ingrowth of connective tissue was marked. Along the central cavity the thick connective tissue border was well organized. There was some blood in the central cavity.

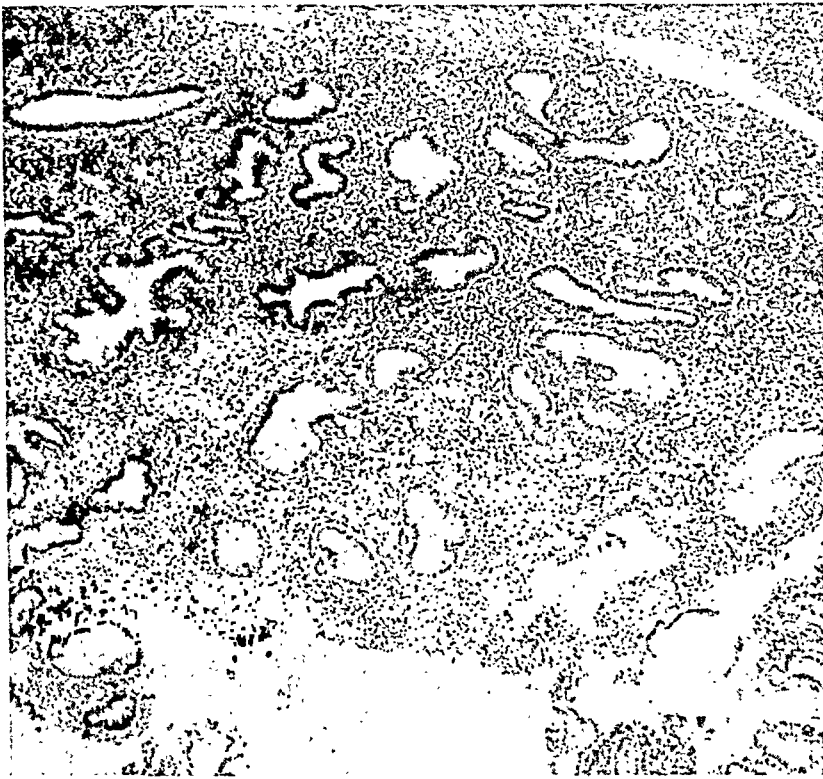


Fig. 10.—The endometrium (Specimen 224) has undergone extensive desquamation. There is considerably less evidence of antecedent secretory activity than in Specimen 325, Fig. 3. The corpus luteum of this specimen is shown in Fig. 8 and Fig. 9.

The theca cells showed the usual grouping and vacuolization. Pyknosis was rare.

Endometrium: Before fixation the thickness of the endometrium varied from 0.2 to 0.4 cm. The surface of the endometrium was irregular and ragged. The loss of tissue was considerable. Many of the glands retained little evidence of secretory activity.

SPECIMEN 215.—Day 1 of cycle. Began to menstruate eighteen to twenty-four hours prior to operation. Age 41 years, para iv, gravida ix. Menstrual history: Onset at 13 years, 26-28-day cycle, five days' flow.

Pathologic diagnosis: Uterine myomas.

Corpus luteum: The dimensions before fixation were 1.5 by 1.2 by 0.8 cm. There was a marked folding of the wall. By far the greater number of the

of degeneration of the granulosa lutein cells was identical to that described by Corner (1945) in day 1 monkey corpora lutea. In this specimen the meager amount of connective tissue extending into the central cavity and the lack of its typical organization as a dense border about the central cavity was unusual in human day 1 corpora lutea, and its significance was not immediately apparent. It resembled more closely the findings in earlier stages of life of the corpus luteum. Specimen 66, removed one hour after the onset of gross bleeding, also showed degeneration of the cells rather uniformly throughout the granulosa lutein layer. The degree of degeneration, however, was considerably less than in Specimen 325. In these two corpora lutea, removed soon after the onset of gross bleeding, there was a distinct variability in the degree of cellular degeneration, although the changes involved all of the cells. A similar picture was seen in some corpora lutea prior to the onset of menstruation. Specimen 149 removed on day 30 of the cycle, prior to the onset of menstruation, showed a marked degeneration throughout. The cells were shrunken, vacuolated, irregular, and many had pyknotic nuclei. The endometrial findings indicated that menstruation will begin shortly. Photomicrographs of this corpus luteum and the associated endometrium are shown in Figs. 7 and 8, *AM. J. OBST. & GYNEC.* 44: 7, 1942.

In some instances degeneration involves only local groups of cells rather than all the cells of the layer. Such is noted before the onset of menstruation (Specimen 255, Fig. 6, *AM. J. OBST. & GYNEC.* 44: 6, 1942, and Specimen 221). Some of the cells in other portions of the granulosa lutein layer of corpora lutea showed evidence of regression only by reduction in cell size. Numerous other cells showed no evidence of degeneration (Fig. 1). These findings were also present in specimens obtained on the first day of menstruation. In Specimens 224 and 215 there were many intact granulosa lutein cells, even though menstruation had begun (Fig. 9). There was considerable variability in the numbers of such cells remaining in various specimens. A localized region of degeneration in Specimen 255 is shown in Fig. 5, and the associated endometrium in Fig. 6, *AM. J. OBST. & GYNEC.* 44: 6, 1942.

In Specimen 13 removed on the first day of menstruation, most cells were reduced in size throughout, and many were in a more advanced state of necrosis. Some cells, however, remained intact, were large, stained well, and had well-stained round nuclei (Fig. 11). The variations in these three corpora lutea removed on day 1 of menstruation were apparent, and the difference between these and the two day 1 cases (Specimen 325, Fig. 2, and Specimen 66) was striking. The finding of granulosa lutein cells with little evidence of degeneration in some portions of the corpus luteum was not unusual in specimens obtained on the first day of normal menstruation.

In some corpora lutea almost all the granulosa lutein cells may remain intact after the onset of menstruation (Specimen 303, Fig. 4, and Specimen 106, Fig. 6). Many of the cells may be reduced in size but staining qualities, shapes, and intact nuclei are retained. Cellular degeneration is minimal. This observation is in distinct contrast to the findings in the rhesus monkey (Corner, 1936 and 1945), and to that found in some day 1 cases, such as Specimens 325, Fig. 2, and 224, Figs. 8 and 9.

It is apparent that there is considerable histologic variation in the granulosa lutein cells during the phase of degeneration of the corpus luteum just prior to and immediately after the onset of menstruation. The variability is noted in the different corpora lutea of this stage and also in the same corpus luteum. The differences that occur between some corpora lutea are shown in Specimen 325 (Fig. 2) as contrasted with Specimens 303 (Fig. 4) and 106 (Fig. 6). Variations occurring in the same corpus luteum are shown in Specimen 224 (Figs. 8 and 9).

Endometrium: The thickest portion of the endometrium after fixation and staining was 0.15 cm. While slough had occurred, the surface of the endometrium was more even than in the other menstruating specimens. No portion of the endometrium was covered with epithelium. The stroma was dense. The glands showed no evidence of present or previous secretory activity (Fig. 12). The gland cells were characteristic of those stimulated only by estrogens.

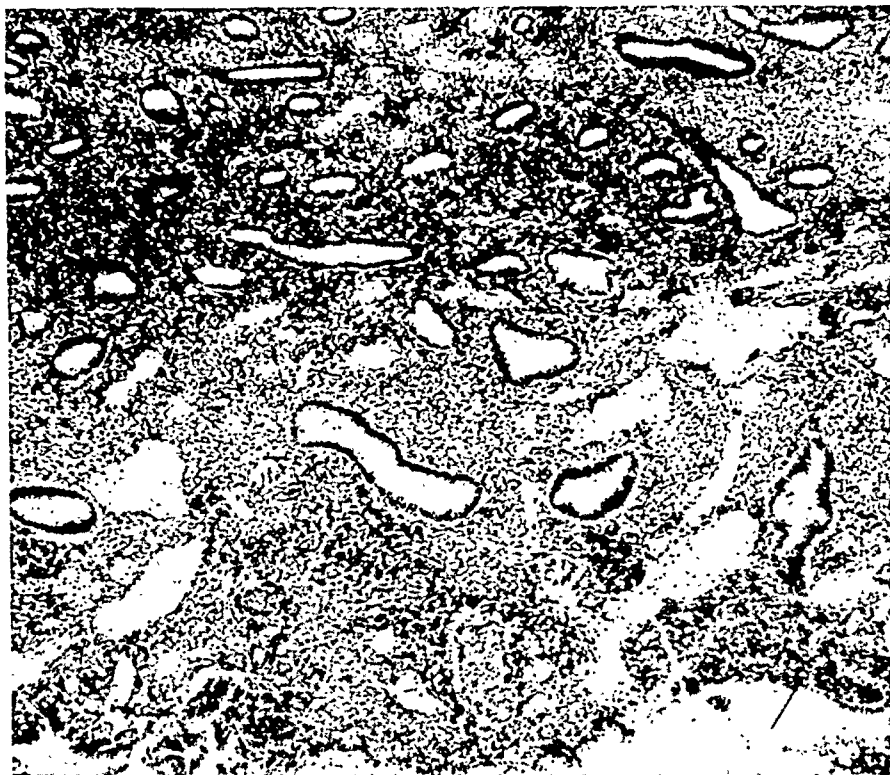


Fig. 12.—The endometrium (Specimen 13) has undergone desquamation in all portions. There is no evidence of antecedent secretory stimulation of the glands. This endometrium is typical of that described as anovulatory menstruation but in this instance a corpus luteum was present (Fig. 11).

Histologic Variations in Granulosa Lutein Cells Immediately Prior to and During Day 1 of Menstruation

In the human corpus luteum, degeneration of the granulosa lutein cells is first noted four to six days before the onset of menstruation (Brewer, 1942). This degeneration is a slow and gradual process, and in its early phases can be a reversible reaction if pregnancy ensues. It is not a process that occurs suddenly at the onset of menstruation, and it does not typically involve all the cells of the granulosa lutein layer uniformly. In the rhesus monkey, Corner (1936 and 1945) concluded that degeneration of the corpus luteum begins at the onset of menstruation, and that the resultant breakdown of cells occurs uniformly throughout. In the corpus luteum of the swine, he (1915) described an early onset of regression and observed that the cells were involved in an irregular way. There may be differences in the degenerative process in various animals.

Histologic variations occur in the degenerative phase of the granulosa lutein cells of the human being. The degenerative process may uniformly involve all of the cells throughout the granulosa lutein layer in some human corpora lutea as described for the monkey and is exemplified by Specimens 325 (Fig. 2) and 66. In Specimen 325, obtained within three hours after the onset of menstruation (as timed by the appearance of gross blood), the picture

menstruation (Fig. 12). It was not an instance of anovulatory menstruation, for a corpus luteum was present in the ovary. The degenerating granulosa lutein cells were uniformly involved as in Specimens 325 and 66, but the degree of degeneration was markedly less. There was considerable variation between this endometrium and the endometria of the other normal day 1 specimens. This specimen varies considerably from that accepted as a normal standard. A definite explanation of this relationship cannot be made on the basis of histology alone. Several possibilities exist. It is possible that the endometrium had been stimulated and that the signs of antecedent secretory activity had disappeared. It is possible that the corpus luteum, while histologically normal and consistent in appearance with corpora lutea of the same stage, was, from a functional standpoint, unable to stimulate the endometrium. It is also possible that the ovarian stimulation was present in adequate amounts, but the endometrium, as an end organ, was unable to respond to normal stimulation. Irrespective of this, three definite statements can be made. One, ovulation had occurred as proved by identification of the rupture point and the fact that a corpus luteum had formed. Two, from a histologic standpoint the corpus luteum was normal for this stage of the cycle. Three, the endometrium was similar to that described as typical of anovulatory menstruation. This specimen well demonstrates the possible error in making a positive statement that ovulation had or had not occurred from a study of the endometrium alone.

The variations in the different endometria and the variations that occur in different regions of the same endometrium just prior to and during the first day of normal menstruation are more considerable than is generally recognized. Bartelmez (1931) described and stressed these endometrial variations in the same and different uteri. In one 28-day case he found that the gland cells contained little glycogen and that the cells lacked secretory evidence. Since there was secretion in the gland lumen indicating antecedent activity, he concluded that the stimulus to secretion had ceased before menstruation into the lumen had begun. In an endometrium obtained eight hours after the onset of bleeding, the glands similarly lacked secretory evidence. He also described two other similar first day cases. In three day 1 cases he found evidence in the endometrium of continued corpus luteum activity after menstruation had begun. Our findings reported here are quite comparable.

A review of the findings in the corpora lutea obtained just before or on day 1 of menstruation indicates that there are variations between the different corpora lutea and also between different regions of the granulosa lutein layer of a single corpus luteum. There are variations in secretory activity and in extent of desquamation in the endometria as well during this period. Not only do these tissues vary among themselves but there is so much variation that an absolute constant pattern cannot be established. A study of the endometrium during this period in the cycle does not accurately reflect the histological picture of the corpus luteum. Similarly, a histologic study of the corpus luteum does not reflect the true state of the endometrium. (Specimens 303, 106, and 13.) It is possible that during this phase of degeneration the histology of the granulosa lutein cells may not reflect a true index of the degree of functional activity of the corpus luteum.

The observations reported here have clinical as well as academic interest. Endometrial biopsies are being more and more frequently studied in endocrine and sterility problems. In the numerous reports the presence or absence of corpora lutea and the qualitative and quantitative functional capacities of the structures are estimated from the histology of the endometrium. On this basis clinical diagnoses are made and treatments instituted. In order that errors are avoided, it is necessary that the histologic variations in the relationship between the corpus luteum and endometrium be evaluated. This is particu-

Variations in the Endometrial Corpus Luteum Relationships Prior to and During Day 1 of Menstruation

The endometrium of Specimen 255 (day 27) had involuted and there was some infiltration of lymphocytes and leucocytes in the superficial portion. (Fig. 6, *AM. J. OBST. & GYNEC.* 44: 6, 1942.) The endometrium of Specimen 221 (day 28) was nearer to the time of onset of menstruation as indicated by the more extensive infiltration of lymphocytes, extravasation of blood, and the presence of small subepithelial hematomas. The granulosa lutein cells of the corpus luteum of Specimen 221, however, showed approximately the same histologic evidence of degeneration as Specimen 255.

The endometrium of Specimen 149 (Fig. 7, *AM. J. OBST. & GYNEC.* 44: 7, 1942) showed less histologic evidence of impending menstruation than Specimen 221, but showed more than Specimen 255. The degree of degeneration of the granulosa lutein cells in Specimen 149 was considerably greater than in Specimen 255 and 221.

These specimens indicate that there are histologic variations in the corpus luteum-endometrial relationships just before the onset of menstruation.

During the first day of menstruation the endometrial findings may vary considerably in the degree of secretory activity as well as in the stage of the menstrual desquamation. Bartelmez (1931) has described such variations, and also has adequately demonstrated the variability in different portions of the same uterus.

In the group of seven first day cases studied, the endometrium in three showed scant slough of tissue. (Specimens 325, 303, and 13.) The endometrial findings in Specimen 325 (Fig. 3) and 303 (Fig. 5) were quite comparable, showing about the same amount of desquamation and comparable degrees of antecedent secretory activity. Specimen 325 was obtained within three hours after the onset of menstruation, while the patient from whom Specimen 303 was obtained had been spotting blood for 18 to 24 hours prior to operation. The granulosa lutein cells of Specimen 325 were uniformly involved in a marked degree of degeneration (Fig. 2). These cells in Specimen 303, however, remained intact and showed little or no evidence of degeneration (Fig. 4). The variability in the endometrial-corpora luteum relationship in these two specimens is apparent.

The moderate desquamation was considerably more and the endometrial gland secretory activity was less in Specimen 215 than in 325, yet the degree of degeneration evident in the granulosa lutein cells of 215 was much less than in 325. Here again the histologic findings indicate a variation in day 1 endometria as well as in the corpus luteum-endometrial relationship.

Extensive endometrial slough was noted in three day 1 specimens (224, Fig. 10; 66; 106, Fig. 7). The degree was more than anticipated in specimens obtained within one to three hours after the onset of menstruation. The degree of desquamation was much greater than in other day 1 cases studied here. The evidence of glandular secretion was approximately the same in these three specimens. The three corpora lutea associated with these three endometrial specimens differed greatly from one another histologically. One (Specimen 66) had considerable cellular degeneration uniformly throughout the granulosa lutein layer. One (Specimen 224) showed only local regions of degeneration in this layer while other regions contained intact cells. One (Specimen 106) showed little or no degeneration of the granulosa lutein cells. Thus, the endometria of these three were histologically similar but the corpora lutea were quite different.

In Specimen 13 the endometrium was thin, showed no evidence of preceding progesterone stimulation, and was typical of that described as anovulatory

A CORRELATION BETWEEN VAGINAL SMEAR AND TISSUE DIAGNOSIS IN 1045 OPERATED GYNECOLOGIC CASES*

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THE vaginal smear as a means of detecting uterine malignancy has been well established by numerous reports¹⁻³⁷ but there are none regarding its value in a hospital devoted exclusively to the care of gynecologic patients. Therefore, it has been the purpose of this study, first to determine the relative value of the vaginal smear in the discovery of cancer as compared to cervical biopsy and curettage; second, it was desired to test the practicability of the method with reference to the amount of special training the pathologist and allied personnel would need and the time they would consume in reading the smears.

Materials and Methods

Vaginal smears, prepared and stained according to the technique of Papanicolaou, were taken from in-patients at this hospital who were to be treated by surgery the following day. In addition, smears were taken from new patients in the out-patient department from whose cervixes biopsies were subsequently taken. All smears were obtained before vaginal examination was performed.

All smears were interpreted by one or another of the authors, who was in complete ignorance of the clinical history and the tissue diagnosis at the time of the reading. In all cases the first smear was recorded as either positive or negative. Such interpretation on any given case was the only one used for the purpose of this study irrespective of whether or not another observer agreed with this initial diagnosis. Every field on every slide was completely examined. In suggestive smears this was done under high-power magnification, whereas it was possible to scan less suspicious smears with the low-power objective, using the high power only on questionable cells. Tissue diagnosis was the entire responsibility of one of the authors (A. T. H.) who used the accepted gross and microscopic criteria of pathologic examination.

Results

The 1,045 cases in this study were divided into three groups. The first group of 1,000 cases comprises those in which the tissue diagnosis is unquestionable. The second group consists of forty-one cases in which this diagnosis might be at variance with that of other pathologists and is, therefore, considered equivocal. The third group contains four cases in which malignancies were encountered elsewhere than in the uterus, cervix or vagina.

Group One.—In Table I are listed the various types of tissue on which is based the pathologic diagnosis. In this group of 1,000 cases there were sixty malignancies, including forty carcinomas of the cervix as shown in Table II; eighteen malignancies of the fundus (Table III); and two carcinomas of the vagina.

*Aided by a grant from the Massachusetts Division of the American Cancer Society, Inc.

larly true since it is rather universally advocated that endometrial biopsies should be taken on day 1 of menstruation and it is at this time that the variations are the greatest.

Endometrial biopsies obtained on day 1 of menstruation do not give accurate interpretations of previous endometrial responses to stimulation. The endometrial tissues are ischemic, partially necrosed or in some regions necrotic, and may be partially or completely inactive from a functional standpoint. In many instances the tissues in some regions reflect antecedent stimulation and activity, while in others such signs of stimulation and activity are greatly diminished or completely wanting. These marked changes have been noted here as soon as one hour after the onset of menstruation. Bartelmez (1931) found them prior to the onset of menstruation.

The endometrium obtained on day 1 of menstruation likewise does not give accurate interpretation of previous corpus luteum secretory activity. It reflects only the diminution or complete cessation of functional activity of that gland which is degenerating or has degenerated. This it does none too accurately as has been shown.

Accurate interpretation of functional activity can be obtained only by studying the endometrium during the actively functioning period of life of the corpus luteum and endometrium.

Biopsies, therefore, must be taken at least four to six days prior to menstruation. This is difficult to do because of variations in time of ovulation and in length of cycles. Determination of time of ovulation by temperature shifts, vaginal smears, hormonal studies, etc., may remove some of the difficulty. If all methods of correct timing fail, repeated biopsies are necessary. One cannot, however, fail to realize the possibility of resultant infection when the uterine cavity is repeatedly invaded at short intervals. The necessity of a diagnosis must be firmly established and the need must offset this possibility before such a procedure is instituted.

Conclusions

1. There are variations in the histologic characteristics of the granulosa lutein cells in different corpora lutea and also in the same corpus luteum just prior to and during day 1 of menstruation. These variations represent normal differences in rate and extent of degeneration in these cells.

2. There are variations in the histologic characteristics of the different endometria and also in different regions of the same endometrium just prior to and after the onset of menstruation.

3. There are also variations in the corpus luteum-endometrial relationships during this period.

4. Because of these variations, interpretations of endometrial biopsies taken near the time of onset of menstruation are particularly subject to error.

5. More accurate conclusions can be reached only by study of endometrial tissues obtained during the active functioning life of the corpus luteum and the endometrium.

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TABLE V. ANALYSIS OF ERRORS

| | MALIG- NANCIES OF CERVIX | MALIG- NANCIES OF FUNDUS | MALIG- NANCIES OF VAGINA | ALL MALIG- NANCIES | BENIGN CASES | TOTAL CASES |
|-----------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|--------------------------|-----------------|----------------|
| Number examined | 40 | 18 | 2 | 60 | 940 | 1000 |
| Incorrect diag- noses by smear | 1 | 3 | 0 | 4 | 11 | 15 |
| Per cent error | 2.5 | 16.6 | 0 | 6.66 | 1.17 | 1.5 |

16.6 per cent. Both vaginal carcinomas had positive vaginal smears. In the total of sixty malignancies there were four false negative smears, which resulted in a total error for the malignant cases of 6.66 per cent.

In the remaining 940 cases which were declared negative by the tissue examination, there were eleven false positive vaginal smears, giving an error of 1.17 per cent. The total combined error resulting from the false negative and false positive smears is thus 1.5 per cent as shown in Tables IV and V.

Group Two.—The material in this group consists of forty-one cases in which the tissue diagnosis might be considered equivocal. This group has been

TABLE VI. CARCINOMA-IN-SITU OF CERVIX

| NO. | SMEAR NO. | DATE OF SMEAR | RESULT OF SMEAR | TISSUE DIAGNOSIS | TISSUE AVAILABLE |
|-----|--------------|---------------------|-----------------------|---|---------------------------------------|
| 1 | V-4 | 11/ 1/45 | Pos. | Carcinoma-in-situ, cervix | Biopsy of cervix |
| | | 12/ 4/45 | Pos. | Carcinoma-in-situ, cervix | Complete uterus |
| 2 | V-65 | 1/28/46 | Pos. | Carcinoma-in-situ, cervix | Biopsy of cervix |
| 3 | V-372 | 5/15/46 | Neg. | Carcinoma-in-situ, cervix; senile endometrium | Complete uterus |
| 4 | V-515 | 7/11/46 | Pos. | Carcinoma-in-situ, cervix; secret. endomet. | Biopsy of cervix, endo. curettings |
| | | 9/16/46 | Neg. | Chronic cervicitis, granulation tis- sue | Biopsy of endocervix |
| | | 1/16/47 | Neg. | Chronic cervicitis with anaplasia | Biopsy of endocervix |
| 5 | V-590 | 8/ 1/46 | Pos. | Carcinoma-in-situ of cervix; chr. endometritis | Complete uterus |
| 6 | V-610 | 8/ 7/46 | Neg. | Carcinoma-in-situ, cervix; squa- mous metaplasia | Biop. cervix; endo. curettings |
| | | 9/26/46 | Neg. | Chronic cervicitis with hyperplasia | Biop. cervix |
| | | 10/10/46 | Neg. | No specimen | |
| | | 1/16/47 | Neg. | Chronic cervicitis with anaplasia | Biop. cervix |
| 7 | V-664 | 8/29/46 | Neg. | Carcinoma-in-situ, cervix; prolif. endometrium | Complete uterus |
| 8 | V-766 | 9/25/46 | Pos. | Carcinoma-in-situ, cervix | Biop. cervix |
| | | 10/17/46 | Pos. | Carcinoma-in-situ, cervix | Biop. cervix |
| | | 1/ 2/47 | Neg. | Chronic cervicitis; anaplasia of re- pair | Biop. cervix |
| 9 | V-828 | 10/17/46 | Neg. | Carcinoma-in-situ, cervix | Complete uterus |
| 10 | V-922 | 11/14/46 | Pos. | Carcinoma-in-situ, cervix with early invasion | Biop. cervix |
| | | 11/22/46 | Pos. | Carcinoma-in-situ, cervix | Complete uterus |
| 11 | V-1037 | 1/ 9/47 | Pos. | Carcinoma-in-situ, cervix | Complete uterus |
| 12 | V-512 | 7/11/46 | Pos. | Carcinoma-in-situ, cervix | Biop. cervix |
| | | 7/18/46 | Pos. | No specimen | |
| | | 7/30/46 | Pos. | Carcinoma-in-situ, cervix (probable invasion) | Complete uterus |
| 13 | V-680 | 8/29/46 | Neg. | Carcinoma-in-situ, cervix | Biop. cervix |
| | | 10/24/46 | Neg. | Carcinoma-in-situ, cervix | Biop. cervix |
| | | 11/26/46 | Neg. | Chronic cervicitis; secretory endo- metrium | Complete uterus |

TABLE I. TISSUES ON WHICH DEFINITE DIAGNOSES WERE MADE

| | |
|---|-------|
| Biopsy of cervix | 152 |
| Complete cervix (amputated) | 38 |
| Complete cervix and uterine curettings | 9 |
| Biopsy of cervix and uterine curettings | 278 |
| Uterine curettings | 70 |
| Biopsy of vagina | 3 |
| Complete uterus | 448 |
| Uterus (supravaginal portion) | 2 |
| Total | 1,000 |

TABLE II. CARCINOMA OF THE CERVIX

| | |
|-------------------------------|----|
| Squamous carcinoma, Grade I | 1 |
| Squamous carcinoma, Grade II | 29 |
| Squamous carcinoma, Grade III | 6 |
| Adenocarcinoma, Grade II | 4 |
| Total carcinomas | 40 |

TABLE III. MALIGNANCIES OF THE FUNDUS

| | |
|---------------------------|----|
| Adenocarcinoma, Grade I | 1 |
| Adenocarcinoma, Grade II | 8 |
| Adenocarcinoma, Grade III | 2 |
| Adenoacanthoma | 4 |
| Carcinosarcoma | 2 |
| Mixed mesodermal tumor | 1 |
| Total malignancies | 18 |

TABLE IV. FALSE NEGATIVE AND FALSE POSITIVE SMEARS

| CASE NO. | SMEAR | PATHOLOGIC DIAGNOSIS | TISSUE |
|----------|-------|--|------------------------------------|
| V-113 | Neg. | Squamous carcinoma of cervix, Grade II | Biopsy of cervix |
| V-444 | Neg. | Early adenocarcinoma of endometrium with hyperplasia and localized anaplasia | Complete uterus |
| V-461 | Neg. | Early adenocarcinoma of endometrium | Complete uterus |
| V-797 | Neg. | Adenocarcinoma of endometrium | Complete uterus |
| V-34 | Pos. | Chronic cervicitis with erosion; menstrual endometrium | Complete uterus |
| V-98 | Pos. | Chronic cervicitis; marked squamous metaplasia and anaplasia; late proliferative endometrium | Complete uterus |
| V-103 | Pos. | Chronic cervicitis with erosion | Biopsy of cervix |
| V-202 | Pos. | Chronic cervicitis with erosion and atrophy | Biopsy of cervix |
| V-722 | Pos. | Chronic cervicitis; proliferative endometrium | Biopsy of cervix; endo. curettings |
| V-946 | Pos. | Chronic cervicitis | Cervix (ant. lip) |
| V-974 | Pos. | Chronic inflammation of fibrous tissue | Biopsy of vagina |
| V-994 | Pos. | Hyperplasia and anaplasia of endometrium | Endo. curettings |
| V-999 | Pos. | Endometrial polyp; atypical menstrual endometrium; chronic cervicitis | Biopsy of cervix; endo. curettings |
| V-1048 | Pos. | Chronic cervicitis with erosion; squamous metaplasia; endometrial polypi | Biopsy of cervix; endo. curettings |
| V-556 | Pos. | Chronic cervicitis; secretory endometrium | Complete uterus* |

*Multiple blocks of cervix failed to locate previously diagnosed carcinoma-in-situ.

In the forty carcinomas of the cervix there were thirty-nine positive vaginal smears and one false negative smear; giving an error of 2.5 per cent. The vaginal smears from eighteen malignancies of the fundus were positive in fifteen cases. False negatives were obtained in three cases, giving an error of

further divided into twenty cases that were diagnosed as *definite* carcinoma-in-situ of the cervix and endometrium respectively (Tables VI and VIII) and twenty-one cases in which there was judged to be in one or the other of these tissues either *probable* or *possible* carcinoma-in-situ (Tables VII and IX). This apparent indecision is the result of an attempt to segregate all such suspicious cases for study and follow-up in order that the true position of carcinoma-in-situ may be more clearly defined. We term them equivocal because many pathologists are in disagreement as to the validity of this diagnosis even when definitely made.

TABLE IX. PROBABLE OR POSSIBLE CARCINOMA-IN-SITU OF ENDOMETRIUM

| NO. | SMEAR NO. | DATE OF SMEAR | RESULT OF SMEAR | TISSUE DIAGNOSIS | TISSUE AVAILABLE |
|-----|-----------|---------------|-----------------|---|--------------------------------|
| 1 | V-12 | 12/11/45 | Neg. | Possible carcinoma-in-situ; anaplasia | Complete uterus |
| 2 | V-247 | 4/25/46 | Neg. | Chronic cervicitis and squamous metaplasia | Biop. cervix |
| | | 8/22/46 | Neg. | Possible carcinoma-in-situ, endometrium; cervical polyp and chronic cervicitis | Biop. cervix; endo. curettings |
| 3 | V-417 | 6/12/46 | Neg. | Probable carcinoma-in-situ | Complete uterus |
| 4 | V-465 | 6/19/46 | Neg. | Probable carcinoma-in-situ and hyperplasia | Biop. cervix; endo. curettings |
| | | 6/28/46 | Neg. | Radium reaction, endometrium | Complete uterus |
| 5 | V-711 | 9/10/46 | Neg. | Possible carcinoma-in-situ and hyperplasia | Complete uterus |
| | | 10/31/46 | Neg. | No specimen | |
| 6 | V-753 | 9/13/46 | Neg. | Possible carcinoma-in-situ and hyperplasia; endometrial and endocervical polyps | Complete uterus |
| 7 | V-821 | 10/15/46 | Neg. | Probable carcinoma-in-situ; endo. and cervical polyps | Complete uterus |
| 8 | V-933 | 11/18/46 | Neg. | Probable carcinoma-in-situ | Complete uterus |

Table VI shows the data in thirteen cases of carcinoma-in-situ of the cervix. It will be noted that in eight instances at least one vaginal smear is positive and in five cases all those taken were negative. It is noteworthy that in Cases 4 and 8 the original biopsies showed carcinoma-in-situ of the cervix with positive vaginal smears, while subsequent biopsies and vaginal smears were negative. Was the malignant tissue completely removed by biopsy?

In Case 6, in which on four occasions the smears were called negative, the tissue diagnosis was also negative on the last two of three biopsies. Hence disagreement was with only the first surgical specimen. The carcinomatous lesion in this case involved mainly the basal layers, suggesting that positive cells may not have reached the surface or for some other reason were prevented from desquamating. Again, did biopsy remove all the affected area?

In Case 7 the vaginal smear was negative and although the original tissue diagnosis was carcinoma-in-situ of the cervix, it was necessary to cut blocks from the entire cervix in order to locate the tiny malignant lesion. The single vaginal smear in this case immediately preceded hysterectomy and was made after the initial biopsy.

In Table VII thirteen cases are listed in which a diagnosis of *probable* or *possible* carcinoma-in-situ of the cervix was made. In only four of these a positive vaginal smear was found. In two of them it may be seen that the smear later became negative and that the tissue diagnosis also became negative, again suggesting complete removal of the pathologic area.

TABLE VII. PROBABLE OR POSSIBLE CARCINOMA-IN-SITU OF CERVIX

| NO. | SMEAR NO. | DATE OF SMEAR | RESULT OF SMEAR | TISSUE DIAGNOSIS | TISSUE AVAILABLE |
|-----|-----------|---------------|-----------------|---|--------------------------------|
| 1 | V-29 | 12/12/46 | Neg. | Probable carcinoma-in-situ, cervix | Biopsy of cervix |
| 2 | V-36 | 1/13/46 | Neg. | Possible carcinoma-in-situ, cervix | Biop. cervix, endo. curettings |
| | | 5/28/46 | Neg. | Chronic cervicitis and metaplasia and hyperplasia | Complete uterus |
| 3 | V-339 | 5/23/46 | Pos. | Probable carcinoma-in-situ and metaplasia | Biop. cervix |
| | | 6/ 6/46 | Neg. | Chronic cervicitis, metaplasia and hyperplasia | Biop. cervix |
| | | 7/ 2/46 | Neg. | Chronic cervicitis, metaplasia and hyperplasia | Complete uterus |
| 4 | V-340 | 5/23/46 | Neg. | Probable carcinoma-in-situ, cervix | Biop. cervix |
| | | 6/ 6/46 | Neg. | Chronic cervicitis, slight anaplasia | Biop. cervix |
| | | 9/12/46 | — | Chronic cervicitis, metaplasia | Biop. cervix |
| 5 | V-356 | 5/28/46 | Neg. | Chronic cervicitis, squam. metaplasia | Biop. cervix |
| | | 6/11/46 | — | Chronic cervicitis, prob. carcinoma-in-situ | Biop. cervix |
| | | 1/ 9/46 | Neg. | No specimen | |
| | | 1/ 9/47 | Neg. | Chronic cervicitis | Biop. cervix (portion only) |
| 6 | V-470 | 6/28/46 | Neg. | Possible carcinoma-in-situ, cervix | Complete uterus |
| 7 | V-528 | 7/17/46 | Pos. | Probable carcinoma-in-situ, cervix | Complete uterus |
| 8 | V-572 | 7/29/46 | Neg. | Probable carcinoma-in-situ, cervix | Complete uterus |
| 9 | V-625 | 8/12/46 | Pos. | Possible carcinoma-in-situ, cervix and metaplasia | Biop. cervix, endo. curettings |
| | | 10/31/46 | Neg. | Chronic cervicitis | Biop. cervix |
| 10 | V-647 | 8/16/46 | Neg. | Probable carcinoma-in-situ, cervix and metaplasia | Biop. cervix |
| | | 11/21/46 | Neg. | Chronic cervicitis, anaplasia | Biop. cervix |
| | | 12/ 5/46 | Pos. | No specimen | |
| 11 | V-788 | 10/ 3/46 | Pos. | Possible carcinoma-in-situ, cervix | Complete uterus |
| 12 | V-790 | 10/ 3/46 | Neg. | Probable carcinoma-in-situ, cervix | Biop. cervix, endo. curettings |
| | | 12/ 5/46 | Neg. | Chronic cervicitis | Biop. cervix |
| 13 | V-852 | 10/24/46 | Neg. | Chronic cervicitis, prob. carcinoma-in-situ | Biop. cervix |
| | | 10/31/46 | Neg. | Chronic cervicitis and paraneurokeratosis | Biop. cervix |
| | | 12/ 9/46 | — | Chronic cervicitis, hyperplasia and anaplasia | Complete uterus |

TABLE VIII. CARCINOMA-IN-SITU OF ENDOMETRIUM

| NO. | SMEAR NO. | DATE OF SMEAR | RESULT OF SMEAR | TISSUE DIAGNOSIS | TISSUE AVAILABLE |
|-----|-----------|---------------|-----------------|---|--------------------------------|
| 1 | V-14 | 12/11/45 | Pos. | Adenocarcinoma-in-situ, endometrium | Complete uterus |
| 2 | V-328 | 5/28/46 | Neg. | Carcinoma-in-situ, endometrium and polyp | Biop. cervix, endo. curettings |
| | | 7/29/46 | — | Endometrial hyperplasia and anaplasia | Complete uterus |
| 3 | V-335 | 5/23/46 | Neg. | Carcinoma-in-situ, endometrium and hyperplasia | Complete uterus |
| 4 | V-364 | 5/29/46 | Neg. | Endometr. polyp with carcinoma-in-situ, hyperplasia and anaplasia | Complete uterus |
| 5 | V-776 | 9/26/46 | Neg. | Carcinoma-in-situ, endometrium | Complete uterus |
| 6 | V-831 | 10/18/46 | Neg. | Carcinoma-in-situ, endometrium | Complete uterus |
| 7 | V-861 | 10/26/46 | Neg. | Carcinoma-in-situ, endometrium | Complete uterus |

method. In view of these facts the method has been found eminently satisfactory for detecting malignancy in the cervix and vagina, but less so in the endometrium.

Attainment of this degree of accuracy required training of personnel and a considerable investment in time devoted to the reading of smears. For the former, each of the examiners, previously experienced in tissue diagnosis, after studying the available literature¹⁻³⁷ spent about two weeks under the intensive tutelage of Mrs. Ruth Graham and her assistants at the Vincent Laboratory of the Massachusetts General Hospital. Such is the training required.

The time consumed in reading varied tremendously and the process at best was much longer and far more tedious than the corresponding tissue examination. It may be roughly estimated that average smears required from fifteen to twenty minutes apiece while in some particularly difficult smears it would require up to two hours. Under conditions other than those stipulated for ourselves, a smear of this type could be labelled "suspicious" and new smears requested. In many cases a second smear might not be so difficult as the first. It must again be emphasized that for the purpose of this study only one smear was examined and that by only one observer, with a subsequent definite negative or positive diagnosis being made. Furthermore, every field of every smear was inspected. Many laboratories would probably not spend this much time, but such a practice would lower the accuracy of the method, especially in early lesions. On several occasions the diagnosis in this study was made from one or two characteristic cells when no other signs were present on the slide. It must be remembered that the technique is actually a random sampling of only a portion of a pool of cells desquamated from all parts of the genital tract.

The study has shown the method to be highly accurate and that it is possible to develop a vaginal smear department of the pathology laboratory within one year. It has proved unexpectedly valuable in the study of early carcinoma and carcinoma-in-situ as well as in the diagnosis of more advanced cases.

Summary

1. A study has been made of 1,045 vaginal smears and the corresponding uterine, cervical and/or vaginal tissue sections. In 1,000 of these cases sixty malignancies of the uterus, cervix or vagina were encountered. Forty-one cases of definite or questionable carcinoma-in-situ were discussed separately.

2. In forty cases of carcinoma of the cervix, thirty-nine were found to have positive smears and one did not; giving an error of 2.5 per cent. In eighteen malignancies of the uterus, fifteen smears were positive and three were negative; giving an error of 16.6 per cent. Two carcinomas of the vagina were encountered and both had positive smears with no error.

3. The total error of positive cases called negative is 6.66 per cent. In the remaining 940 cases with negative tissue sections there were eleven false positive vaginal smears; giving an error of 1.7 per cent. The total combined error of false positive and false negative smears is thus 1.5 per cent.

In Case 10 the last vaginal smear, positive, was taken late in the study. It will be of interest to note what the next biopsy of this cervix will show.*

The cases in Table VIII consist of seven patients in which a definite diagnosis of adenocarcinoma-in-situ of the endometrium was made. Only one positive smear was found in this group. This indicates the difficulty of an accurate smear diagnosis in this type of lesion, which is not surprising since this lesion that is not considered valid by many qualified pathologists, tends to be deeply situated and is thus less apt to cast off cells directly into the uterine cavity. It will be noted that even in frank carcinomas of the endometrium there was less correlation with the vaginal smear.

Table IX gives the data from eight cases in which a diagnosis of *probable* or *possible* carcinoma-in-situ of the endometrium was made. No positive smears were encountered, a fact which is again not surprising in view of the questionable nature and location of the lesion. In Case 2 the patient has since become pregnant. This would indicate a fairly healthy endometrial status, although the possibility of an early carcinoma's having been completely removed by curettage cannot be ruled out.

The smear results from all cases of carcinoma-in-situ are shown comparatively in Table X.

TABLE X. CARCINOMA-IN-SITU RESULTS

| | | NUMBER OF CASES | POSITIVE SMEARS | NEGATIVE SMEARS |
|--------------|-------------|--------------------|--------------------|--------------------|
| Definite | Cervix | 13 | 8 | 5 |
| | Endometrium | 7 | 1 | 6 |
| Questionable | Cervix | 13 | 4 | 9 |
| | Endometrium | 8 | 0 | 8 |

Group Three.—The four incidental malignancies in this group are not included with the others because their diagnoses do not seem to be applicable to the vaginal smear technique. Pathologic examination in these cases revealed lesions respectively of the Fallopian tube, bladder, urethra and vulva. Positive smears in all four indicate that malignant cells from such sources may be carried into the vagina.

Discussion

The value of the smear as compared to tissue diagnosis is manifest in the tabulation of errors shown in Table V. Since the method in actual daily application would undoubtedly provide the observer with clinical information which the authors purposely avoided, its accuracy could be reasonably expected to increase, largely by the avoidance of false positive readings. It is further significant that only one of the four false negative readings (V-797) occurred because malignant cells were initially unrecognized although present, whereas the other three have been repeatedly re-examined without the discovery of malignant cells, thus indicating an irreducible error inherent in the

*From comparison of the corresponding smears and tissue specimens in these cases it may be that in many instances the first biopsy either completely removed the carcinomatous area or instigated a more intense reparative reaction which resulted in normal healing. This would imply that the carcinoma-in-situ is a result of prolonged subminimal stimuli with abortive attempts at healing which go astray. When a more violent stimulus is provided, such as that incident to biopsy, a more normal repair process ensues and results in the formation of normal tissue.

THE RELATIONSHIP BETWEEN SEX HORMONES AND EXPERIMENTALLY INDUCED TUMORS IN RATS*

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WHILE the etiology of cancer is obscure, the number of agents indicated as factors in carcinogenesis is extensive. Various substances have been incriminated in the causation of cancer as a result of the accumulation of a vast amount of circumstantial evidence noting the prevalence and repeated occurrence of malignant neoplasms in different occupational trades. For instance, it was shown in the investigation of human occupational cancers that certain coal tar derivatives were carcinogenic. Thus, the classical example of scrotal carcinomas in chimney sweeps demonstrated the role of occupational hazards in cancer.¹ Although the inciting factor could only be suspected, it was the epochal work of the Japanese workers that established the role of coal tar in carcinogenesis when applied locally in the production of skin cancer.² Later, extractions of the carcinogenic principle led to the isolation of a chemically pure carcinogenic compound of the 1:2 benzanthracene series, in particular 3:4 benzpyrene,^{3, 4} the only potent carcinogenic compound found to be present in coal tar. The manner in which tumorigenesis is initiated by the coal tar derivative has not yet been determined.

In view of the experimental production of carcinogenesis by certain hydrocarbons of the pentacyclic aromatic groups, it has been suggested that malignant neoplasms arising spontaneously in the organism may likewise be induced by the endogenous formation of cancer-producing hydrocarbons arising from the abnormal metabolism of cholesterol or of the bile acids. The eventual demonstration of a degradation product, methyleholanthrene, from a naturally occurring constituent of the organism, bile acids, gave support to the hypothesis that potent carcinogens may be evolved in the body.⁵

Further proof that endogenous substances, such as methyleholanthrene, may be related to or arise from substances occurring naturally in the organism, is the apparently striking fact that the 1:2 benzanthracene derivatives belong to the cyclopentane ring group characteristic of the naturally occurring sterols and sex hormones.⁶ The role of the sex steroids, particularly estrogens, in inciting abnormal growth and neoplasia of the generative tract of the female, while long suspected, has only been proved experimentally in the past decade or two. The evolution of the concept that estrogens are important in the initiation of carcinogenic changes in the female reproductive tract is interesting to follow. The first line of evidence was observed early at the turn of the century when bilateral oöphorectomy was first performed as an ameliorating measure in carcinoma of the breast.⁷ While this procedure has since been frequently performed and is still carried out by some modern surgeons, it has been generally abandoned. Recurrent waves of enthusiasm

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4. Four incidental malignancies were encountered including one each from the bladder, urethra, vulva and Fallopian tube.

5. Eight positive and five negative smears were encountered in thirteen carcinomas-in-situ of the cervix. Only one positive smear was found in seven carcinomas-in-situ of the endometrium.

6. Four positive smears were encountered in thirteen questionable carcinomas-in-situ of the cervix. No positive smear was found in eight questionable carcinomas-in-situ of the endometrium.

Conclusions

The vaginal smear method is an accurate and valuable adjunct to a gynecologic clinic. Although time-consuming, it can be satisfactorily carried out in a pathology laboratory equipped and staffed with the necessary trained personnel.

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ing between these two general groups in the initiation of carcinogenesis. Observations are presented on the influencing effect of various endocrine steroids on tumors induced by methylcholanthrene or benzpyrene when these latter substances are administered either subcutaneously or directly into the uterus. Experimental findings are also recorded on the influence of various endocrine preparations administered chronically not only on the production of chemically induced tumors, but also on other organs of the injected animal. The effect of the different steroid hormones on subcutaneously transplanted sarcomas is also described.

Procedure

As a base line for our studies and to learn some fundamentals about the problem thirty young white rats, commercially obtained, were employed in preliminary experiments. Varying quantities of methylcholanthrene in dosages from 10 to 50 mg. were administered subcutaneously in one to several injections. In all, circumscribed sarcomas developed within three to six months at the site or sites of injection (Fig. 1). The sarcomas did not metastasize. The tumors grew to relatively enormous size (Fig. 1). Occasionally ulcerations developed superficially. The rats were sacrificed 8 to 12 months after the start of the experiment. In several rats methylcholanthrene was injected directly into the uterine horn with a view toward inducing local tumorigenesis in the uterus. The horn was tied off and threads passed through various parts to traumatize the tissue. Estrogens or estrogen and progesterone were then administered in chronic doses for several months, along with occasional subcutaneous injections of methylcholanthrene. The subcutaneously administered methylcholanthrene served a twofold purpose: (1) to further influence the proliferative propensities of the sex-related organs, and (2) to act as control to the methylcholanthrene introduced into the uterus. Sarcomas developed at the sites of subcutaneous injection of methylcholanthrene, but no sarcomas were observed to develop in the uterus in any instance.

A typical protocol is that on rat No. 8 (methylcholanthrene injected into the right horn) presented in Table I.

TABLE I

| | |
|---|---|
| 1/14/39 | 10 mg. methylcholanthrene injected into right uterine horn (horn tied). |
| 1/16/39 | 80 r.u. |
| 1/18/39 | 80 r.u. |
| 1/21/39 | 50 r.u. |
| 1/24/39 | 50 r.u. |
| 1/27/39 | 60 r.u. |
| 1/30/39 | 70 r.u. |
| 2/ 6/39 | 70 r.u. |
| 2/10/39 | 80 r.u. |
| 2/13/39 | 120 r.u. |
| 2/19/39 | 130 r.u. |
| 2/20/39 | 130 r.u. |
| 3/ 7/39 | 425 r.u. |
| 3/15/39 | 400 r.u. |
| 3/23/39 | 365 r.u. |
| 4/ 8/39 | 100 r.u. |
| 5/ 4/39 | 40 r.u. |
| 5/ 7/39 | 40 r.u. |
| 2,290 r.u. over period of 5 months. | |
| 8/ 4/39 | Tumor 3 by 3 cm. in size on right dorsum—appeared about 7/15/39 |
| 10/ 1/39 | Second tumor present on left dorsum—appeared about 9/20/39 |
| Autopsy performed one year after start of experiment. | |

for the operation^{8,9} nevertheless set in only to be discarded again and relegated to the limbo of therapeutic dreams. It appears, then, that long before the discovery and identification of estrogenic hormone, the ovary was thought to be an agent responsible in some way for the development of certain malignancies of the breast and genital tract.

Credence was lent to the assumption of an ovarian-breast tumor relationship by the findings of Leo Loeb who reported in 1907¹⁰ that the incidence of spontaneous breast cancer in certain strains of mice was very high in the female, nil in the male. Furthermore, in 1916¹¹ Loeb and his co-workers demonstrated that ovariectomy at an early age (i.e., before six months) prevented or greatly reduced the incidence of mammary carcinoma in strains of mice which normally had a high incidence. If spaying, however, was performed after the eighth month there was no appreciable reduction in incidence. This work was confirmed and extended by Cori.^{11a} It remained for Lacassagne to show that mammary cancer could be induced in male mice following injections of estrogens if the strain employed belonged to one in which the females had a high incidence of spontaneous mammary cancer.¹² His observations permitted the conclusion that the genetic factors for cancer, present in both males and females, became operative only after the mammary glands had grown in response to estrogenic stimulation.

While the importance of estrogens as carcinogenic agents in certain small animals was definitely established by Lacassagne's experiments, it must not be forgotten that the hereditary or the genetic susceptibility must exist. Slye, Little, Andervont, and others later demonstrated the role of genetics alone and in combination with other factors in the role of spontaneous cancer in mice.¹³⁻¹⁷ Other nongenetic factors have also been incriminated as playing important roles in spontaneous mammary cancer. For instance, it was found that when females of a high cancer strain were bred with males from a low cancer strain, the female offspring had a high incidence of mammary cancer. When, however, the females of a low cancer strain were bred with males from a high cancer strain, the female offspring showed a low incidence of mammary cancer. Later, Bittner¹⁸⁻²⁰ showed that this nongenetic element in mammary carcinogenesis is the milk factor. If, for example, the young from cancer susceptible mothers are fostered by cancer resistant mothers, the incidence of subsequent mammary cancer is reduced, and vice versa.

From the experimental work quoted, it seems that mammary cancer is caused by the conjoined action of three factors:^{19,20} (1) estrogens, (2) a nongenetic agent transmissible to the offspring from the mother's milk, and (3) a genetic factor which controls to some extent the susceptibility of the mammary tissue to neoplastic changes by the other two factors.

The factors just enumerated do not apply to carcinogenesis of other primary and secondary sex organs. Cervical cancer could be produced in mice if estrogen therapy was prolonged for at least a year at a time.²¹⁻²⁴ It was noted that cervical cancer could be induced in strains of mice resistant to mammary cancer. These mice, however, exhibited poor tolerance to the chronic estrogenic treatment at levels effective for cervical carcinogenesis.²² The "milk factor," so important in determining the incidence of mammary cancer, apparently had no relation to incidence of cancer of the cervix following administration of estrogens.²⁴ In this connection it must be recalled that cervical cancer, unlike mammary cancer, does not appear spontaneously in mice.

In view of relative similar chemical configuration of the carcinogenic hydrocarbons and the sex steroids and their respective roles in carcinogenesis, the following studies were undertaken to establish the possibility of synergism exist-

A). *The effect of implantation of pellets of benzpyrene into the uterine horn on tumorigenesis and the influence of various hormonal pellets implanted into the opposite horn.*—

Studies were undertaken to determine the direct tumorigenic effect of benzpyrene upon the uterine mucosa. Accordingly, pellets of benzpyrene were implanted into the uterine horn. One to two pellets weighing 10 to 15 mg. (total) were implanted into the left uterine horn. The influencing effects of the sex steroids were also ascertained by direct implants of 13 to 17 mg. pellets of testosterone, progesterone, and estradiol into the lumen of the opposite uterine horn.

Control animals received only pellets of benzpyrene. Animals of both groups were ovariectomized prior to implantation of the pellets. At the time of implantation, the uterine horns were threaded with black silk proximal and distal to the pellets in order (a) to maintain adequately the pellets and prevent their extrusion, and (b) to provide an additional means of irritating the uterine mucosa and establish thereby a more "fertile" ground upon which the carcinogenic agents might act.



Fig. 3.—Pyometria and squamous cell metaplasia following intrauterine administration of methylcholanthrene ($\times 125$).

Daily vaginal smears, via pipette lavage, were taken throughout the experimental period. Frequent cornification of the smear was observed in the animals receiving implants of estradiol pellets. Smears made from other animals in the remaining group showed the typical diestrus smear characterized by a predominance of leucocytes in a typically mucous medium. All animals were autopsied one hundred eighty days after implantation of pellets.

In no instance, in either the experimental or control series, were intrauterine pellets of benzpyrene productive of any neoplastic changes. Some of the steroids produced marked gross and morphologic changes (Table II). The pellets of progesterone produced no striking anatomical changes and in every case were entirely absorbed in the period of one hundred eighty days. The only discernible effect of the pellets of testosterone was to bring about a diminution in the size of the hypophysis of the implanted animal. Sixty to 75 per cent by weight of the pellets were absorbed. In contrast, marked changes were produced in the animals receiving intrauterine implantation of

Table I summarizes the substances administered to this rat. The tumors at the sites of injection were large. No breast tumor development was discernible. The rat was autopsied twelve months after start of the experiment. The right uterine horn was distended (Fig. 2). Histologic examination revealed a pyometrium and squamous cell metaplasia of the uterine mucosa of the right horn (Fig. 3). Sections of the ovaries, liver, kidney, lung, and left horn of the uterus failed to show any noteworthy changes. Cervical sections revealed marked epithelial hyperplasia. Histopathologic study of the tumor tissue revealed spindle shaped cells growing autonomously with marked cellular derangement, frequent and bizarre mitotic figures and multinucleated giant cells. Large, thin-walled arterioles were observed throughout the section. This rat received over 2,200 r.u. of estrogenic substance over a period of five months.

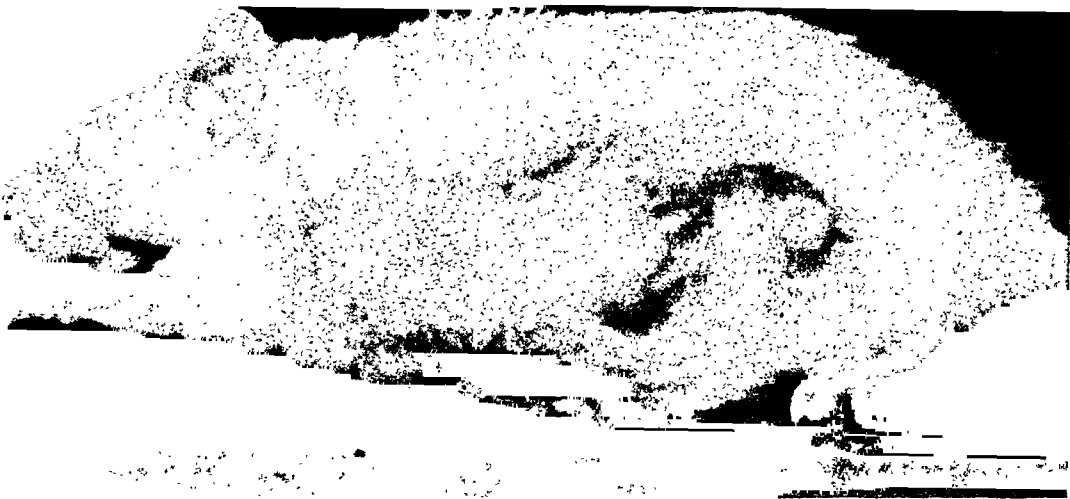


Fig. 1.—Methylcholanthrene induced sarcoma.

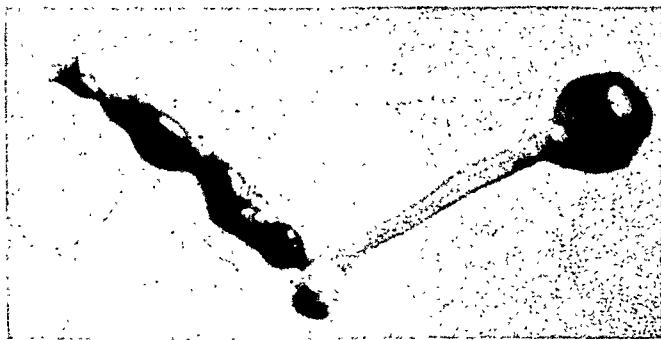


Fig. 2.—Note distended right uterine horn twelve months after intrauterine administration of methylcholanthrene.

It was apparent from our preliminary studies that methylcholanthrene could produce sarcomas in every instance at the subcutaneous site of injection. However, when introduced into the uterine horn and in spite of accompanying trauma and prolonged administration of estrogens, tumorigenesis of the uterine horn could not be obtained other than squamous cell metaplasia and some suggestive precancerous lesions of the cervix. It was decided to continue with a more systematic study employing benzpyrene along with various endocrine preparations. This study followed several directions:

The relationship of various endocrine preparations to the growth of transplanted sarcomas was tested by administration of estradiol dipropionate, desoxycorticosterone acetate, progesterone, testosterone propionate and thiouracil to the animals receiving the transplants of the sarcomatous tissue. The following doses of these preparations were administered every second day in 0.05 c.c. of sesame oil in the case of the steroid hormones, and in 0.1 c.c.

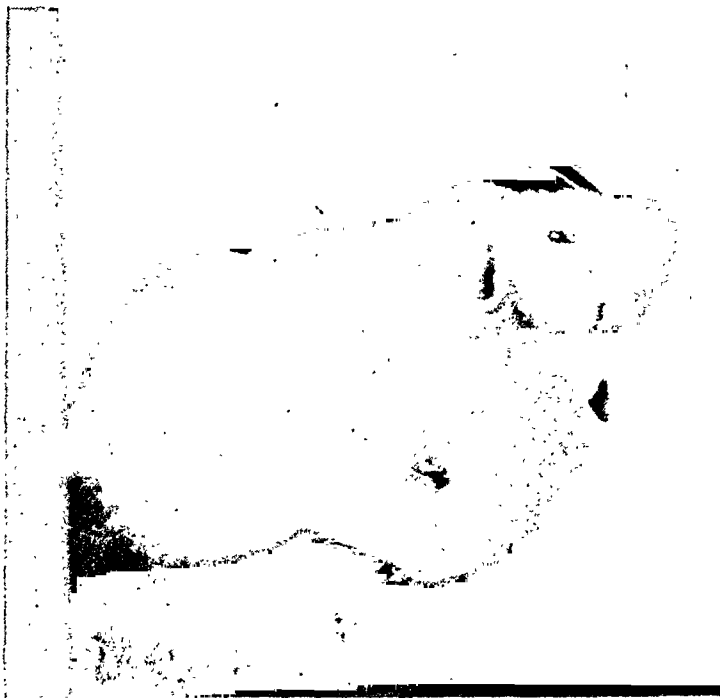


Fig. 4.—Growth of sarcoma thirty-six days after transplantation of benzpyrene induced sarcoma (third generation).

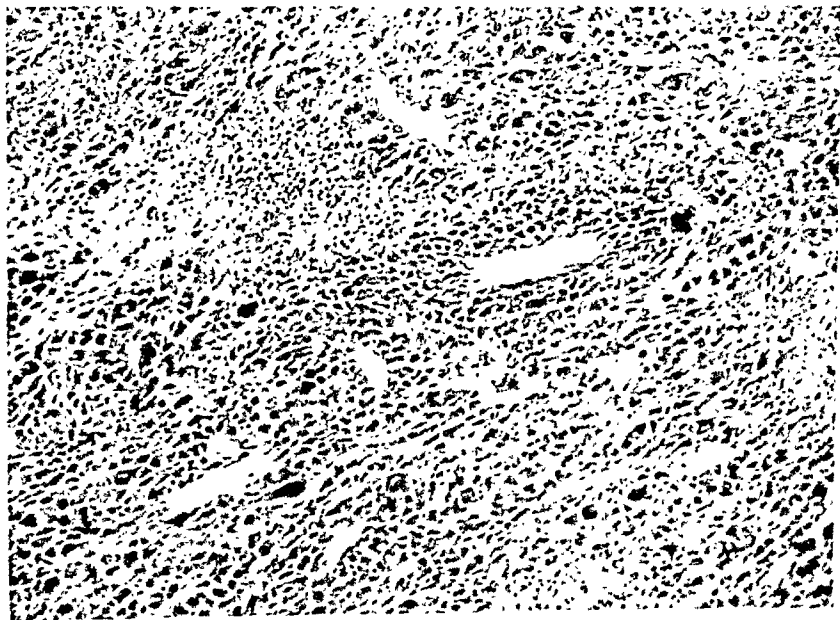


Fig. 5.—Histologic section of growth of sarcomatous tissue transplanted five weeks previously. Tissue transplanted from benzpyrene-induced sarcoma. Sarcoma weighed 24 grams. Note characteristic large, thin-walled capillaries, multinuclear giant cells and cellular disarrangement.

pellets of estradiol (Table II). The uterine weight was increased threefold over that of the controls. There was also marked hypertrophy of the adrenal glands and both hypertrophy and hyperplasia of the hypophysis. Morphologically, the changes in the pituitary gland were shown to be predominantly ones of chromophobic activity. Fifty to 75 per cent by weight of the pellets of estradiol were absorbed after one hundred eighty days.

TABLE II. BENZPYRENE IMPLANT INTO LEFT HORN OF UTERUS (WITH HORMONE IN OTHER HORN (RIGHT). ANIMALS AUTOPSIED 180 DAYS AFTER IMPLANTATION

| TREATMENT | UTERUS (MG.) | ADRENAL (MG.) | PITUITARY (MG.) | THYROID (MG.) |
|-----------------------------|-----------------|------------------|--------------------|------------------|
| Benzpyrene | 255 (3)* | 39 (3) | 17.2 (3) | 13.3 (3) |
| Benzpyrene and progesterone | 221 (3) | 45 (3) | 17.8 (3) | 12.0 (3) |
| Benzpyrene and testosterone | 235 (2) | 35 (2) | 13.2 (2) | 13.5 (3) |
| Benzpyrene and estrogen | 734 (1)† | 67 (2) | 71.7 (2) | 11.5 (2) |
| Control-normal‡ | 507 | 55 | 13.0 | 13.0 |
| Control-castrated‡ | 135 | 58 | 13.5 | 14.3 |

*Figures in parentheses indicate number of animals.

†One uterus, large and bulky, with numerous adhesions, could not be dissected free. Weight estimated between 500-700 mg.

‡Control data represent average weights of 25 rats.

B). Effect of benzpyrene injected subcutaneously and the influence of estrogens or estrogens and desoxycorticosterone on the benzpyrene induced tumors.—

The sarcoma-inducing qualities of benzpyrene were ascertained by injecting a total dose of 20 mg. of benzpyrene in sesame oil over a period of forty days. The benzpyrene was administered subcutaneously every second day in 1 mg. doses contained in 0.05 c.c. sesame oil. The influence of estradiol dipropionate and combined injections of both estradiol dipropionate and desoxycorticosterone acetate upon the induction of sarcoma by benzpyrene was likewise determined. Estradiol dipropionate (0.025 mg.) and desoxycorticosterone (0.25 mg.) were administered in 0.05 c.c. of sesame oil every second day. The endocrine preparations did not appear to accelerate or diminish the rate of growth of the benzpyrene induced tumors. Sarcomas developed at the site of injection of benzpyrene in all the animals within ninety to one hundred twenty days. No demonstrable difference in relation to time of appearance, rate of growth and microscopic appearance of the tumor was observed in the sarcomas produced by benzpyrene and those observed in animals receiving benzpyrene and steroid preparations. The sarcomas, however, varied greatly in size in each individual group and ranged from 10 to 92 Gm. in weight. In some animals the tumors attained 50 per cent of the weight of the animal. Grossly these growths were sharply circumscribed, well encapsulated and showed no gross or microscopic evidence of metastases. Microscopically, the sarcomas were identical to those induced by methylcholanthrene (Fig. 8).

C). Transplantation of benzpyrene-induced tumors and the influence of various hormones on transplantability.—

The tumors from all three groups of animals described above were readily transplantable and the transplantations were carried for three to six generations (Figs. 4 and 5). The tumors were transplanted into adult female rats weighing between 200 to 250 Gm. within three to five minutes after autopsy. The donor animals were killed by ether asphyxiation. The tumors were dissected from the animal, weighed, and divided into small rectangular portions about 2 by 4 by 10 mm. in size and weighing 50 to 75 milligrams. Two or three tumor slices were implanted subcutaneously into the scapular region of the recipient animals. The animals implanted were divided into two groups: (1), the experimental, received daily injections of some endocrine preparation; (2), the uninjected control group.

or inhibited the rate of growth of the transplanted sarcoma over and above that observed when therapy was initiated simultaneously with transplantation.

The data, while meager in some experiments, indicate upon analysis that estradiol had an inhibiting effect on the rate of growth of the transplanted sarcomas (Table III). In addition to a decreased incidence of successful takes as compared to the controls, there was also a significant reduction in weight of the transplanted sarcoma in the estrogen treated animals over that observed in the control groups. The weight of the sarcomas in the animals treated with



Fig. 7.—Squamous cell metaplasia of endometrium of uterus after administration of estrogen for five months ($\times 145$).

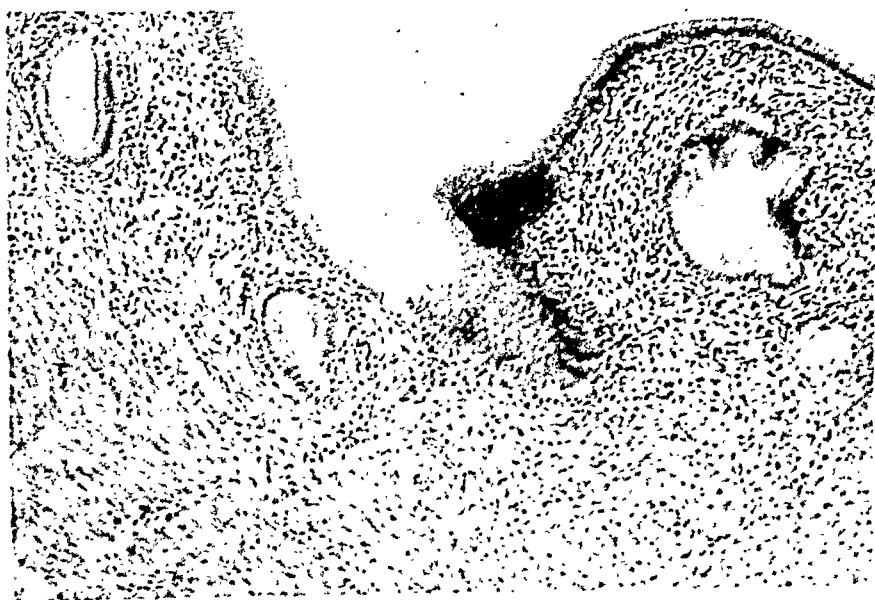


Fig. 8.—Area of anaplasia of endometrium of uterus in rat receiving estrogens for 55 months. Note the abrupt change from columnar epithelium to an area of squamous cell type. Many mitotic figures are to be noted in this area which is suggestive of anaplastic change.

water for the thiouracil; estradiol dipropionate .025 mg., desoxycorticosterone acetate 0.5 mg., progesterone 0.5 mg., testosterone propionate 0.25 mg., thiouracil 10 mg. The percentage of successful transplantations ranged from 79 per cent for the controls to 40 per cent in the animals receiving progesterone.

In addition to treating the animals with various hormones at the time the transplants were made, the effects of pretreatment with estradiol dipropionate, testosterone propionate, desoxycorticosterone, and progesterone upon the growth of the transplanted sarcoma was observed. The recipient animals in this group received endocrine therapy two to four months before the tumor transplants were made with therapy continuing after implantation. The dosages of these preparations employed in the pretreatment phase of the experiment were similar to those described above. In this latter group of animals there was no evidence to show that the steroids administered in this manner enhanced



Fig. 6.—Chromophobic adenoma induced in pituitary gland after 7.5 months of estrogen administration.

TABLE III

| TREATMENT | DAYS TREATED | OVARY | ADRENAL | THYMUS | UTERUS | THYROID | PITUI- TARY | TUMOR | PER CENT OF TU- MOR TAKE |
|--------------------------------------|----------------------------|-------------------------|-------------------------|--------------------------|--------------------------|-------------------------|--------------------------|-------------------------|--------------------------------------|
| Estrogen | 167.90 ± 3.86* (24)† | 26.40 ± 0.82 (24) | 68.70 ± 0.98 (24) | 73.00 ± 1.57 (22) | 622.50 ± 6.71 (23) | 16.20 ± 0.78 (24) | 120.40 ± 4.73 (24) | 44.80 ± 2.31 (12) | 50% |
| Progesterone | 121.60 ± 16.86 (5) | 49.60 ± 4.41 (5) | 88.60 ± 9.68 (5) | 101.40 ± 14.18 (5) | 351.20 ± 29.18 (5) | 18.20 ± 1.05 (5) | 14.50 ± 1.15 (5) | 155.00 ± 3.57 (2) | 40% |
| Testosterone propionate | 92.30 ± 8.92 (6) | 51.80 ± 11.96 (6) | 47.70 ± 3.04 (6) | 122.20 ± 13.83 (6) | 270.50 ± 8.04 (6) | 16.00 ± 0.56 (6) | 10.70 ± 0.28 (6) | 134.00 ± 1.88 (3) | 50% |
| Desoxycorticos- terone acetate | 68.80 ± 3.89 (8) | 54.40 ± 3.06 (8) | 76.50 ± 1.39 (8) | 86.30 ± 9.36 (8) | 337.50 ± 23.50 (8) | 16.80 ± 0.52 (8) | 13.10 ± 0.22 (8) | 109.70 ± 7.29 (6) | 75% |
| Control | 80.00 ± 2.05 (33) | 62.40 ± 1.11 (33) | 72.40 ± 0.67 (33) | 94.20 ± 1.65 (33) | 352.70 ± 6.07 (33) | 16.00 ± .095 (33) | 11.60 ± 0.10 (33) | 79.90 ± 1.76 (26) | 79% |

*Standard error.

†Figures in parentheses indicate the number of animals.

been shown that estrogens play some role in the production of a cancerous state of the mammary and occasionally the uterine (cervical) tissue of mice susceptible to cancer, estrogenic substances play little or no part in mice refractory to cancer and none in larger animals.²⁸ Evidence of carcinogenic action of estrogens in the human female is meager and at times is only suggestive. Sporadic reports have shown that estrogens or estrogenic activity may be indicted in the pathogenesis of certain cases of breast or uterine carcinoma.²⁹⁻³¹ These reports are of necessity poorly controlled and the conclusions could well be challenged. In this respect it is interesting to speculate concerning the doses employed in the rat and the comparative dosage in the human. On the basis of the dosage given to the rat in this experiment the amount to be given to the human, calculated in the table below, would be in line of such excessive doses as 6.5 mg. administered every second day for a period of 14.5 years (Table IV).

TABLE IV. DOSE OF ESTRADIOL RELATIONSHIP BETWEEN THE RAT AND THE HUMAN

| | LIFE SPAN | WEIGHT | DOSE Q 2ND DAY | TIME ADMINISTERED |
|-------|-----------|-----------|-------------------|----------------------|
| Rat | 3 years | 0.25 kg. | 25.0 gamma | 8.0 months |
| Human | 65 years | 65.00 kg. | 6.5 mg.* | 14.5 years† |

*Dose based on that given to rats and on weight relations of rat to human.

†Time estimated on total time of hormone administration to rats and relation of life span of rat to that of human.

Another line of evidence to consider when evaluating the role of estrogens in the etiology of neoplasms is the contradictory results observed in those cases of breast carcinomas that had been treated with stilbestrol. Synthetic estrogens have been reported to bring about temporary retardation or partial regression of the neoplastic growth.³² These observations have been confirmed.³³ Thus it was shown that of a total number of 69 patients under the age of 51 given stilbestrol for advanced breast cancer, 43 did not improve while some showed spectacular improvement. Stilbestrol administered to 52 patients over 58 years of age resulted in improvement in 17 cases and spectacular improvement in six or seven cases. In this latter group in some patients there was complete disappearance of the fairly advanced disease.³⁴ These findings have been substantiated recently in a 91-year-old woman with a breast carcinoma.³⁵ The carcinoma subsided with no evidence of swelling after six months of treatment with daily doses of 3 mg. of diethylstilbestrol. It has also been shown that secondary sarcomatous deposits in the lung of a young woman disappeared completely two years after stilbestrol treatment had been instituted.³⁶

Summary

The effect of various steroid hormones upon the induction of carcinogenesis by methylcholanthrene and benzpyrene was studied. Subcutaneous and intra-uterine administration of the carcinogenic agents was made by injecting either oil solutions or suspensions of the carcinogen in lard and by implantation of compressed pellets of benzpyrene. No neoplastic changes were observed in rats receiving intrauterine application of either one of the coal tar derivatives

estradiol dipropionate was only 57 per cent that of the neoplasms of the control animals. While administration of progesterone, testosterone propionate, and desoxycorticosterone acetate caused a 34 to 94 per cent increase in weight of the sarcoma over that attained in the control rats, there was a decreased incidence in tumor takes in those animals receiving progesterone and testosterone propionate. In contrast to the animals receiving intrauterine implants of pellets of progesterone and estrogen, subcutaneous administration of estradiol dipropionate in oil caused no adrenal hyperplasia, while progesterone in oil caused hypertrophy of questionable significance. Testosterone propionate injections resulted in a reduction in size of the adrenal glands. Estradiol, as has been reported, resulted in marked hypertrophy of the pituitary gland (Fig. 6). The hypertrophy of the hypophysis was due mainly to hyperplasia of the chromophobic elements forming in many instances a chromophobic adenoma. Estrogens also caused a marked hypertrophy of the uterus and in many cases squamous cell metaplasia of the mucosa was observed (Fig. 7). Metaplasia, however, was never observed with chronic administration of progesterone, desoxycorticosterone acetate or testosterone propionate. In one instance a localized area of anaplastic change in the uterine mucosa was found (Fig. 8). Definite malignant changes in the breasts were observed in only one rat receiving estrogens, although many animals showed proliferative changes indicative of cystic changes in the acini of the breast.

Discussion

From an analysis of our studies it appears that the estrogenic hormone is a strong proliferative hormone and that methylcholanthrene and benzpyrene applied directly to the uterine mucosa could not induce out and out malignant changes in the uterine horn, despite administration of chronic doses of estrogenic substance. In this respect Castellano and D'Amour did obtain occasional malignancies in their experiments when pellets of methylcholanthrene were implanted into the uterus.²⁵ However, no discussion of the microscopic picture of the neoplasms was presented, nor were the malignancies described. Their period of observation, however, was longer—a minimum of one year. In addition, workers from the same laboratory reported a statistically significant hastening of the appearance of the subcutaneous methylcholanthrene-induced tumors under the influence of pregnancy urine and pregnant mares serum (PMS).²⁶ PMS appeared to sustain a greater effect. In our study, aside from epithelial metaplasia of the endometrium and epithelial stimulation of the cervix, no carcinomatous changes of the reproductive tract were observed. Geschickter was able to produce carcinoma of the breast in rats by injection of 200 gamma over 100 days.²⁷ This dosage was far greater than which we used.

There can be no doubt that estrogens, administered over a relatively long period of time to certain experimental animals, are capable of inducing malignant changes in a substratum hereditarily susceptible to cancer. An impression has been created, however, that what strictly applies to animal experimentation also applies to man. Thus the implications of the neoplastic tendencies of estrogenic or estrogenic-like substances in certain susceptible animals have led, and properly so, to the cry for caution in the empirical use of long-continued, massive dosage of estrogens clinically. Although it has

RELATIONSHIP BETWEEN ERYTHROCYTE SEDIMENTATION RATE, SLUDGED BLOOD, AND PLASMA PROTEINS DURING PREGNANCY*†

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AMONG the several factors which have been associated with changes in erythrocyte sedimentation rate are these: Fåhræus¹ noted increased rouleaux formation and higher plasma fibrinogen and globulin values in blood from patients with increased sedimentation rates; and it was demonstrated subsequently, by Monaghan and associates,² that sedimentation rate depended upon constituents contained within blood plasma. In fact, in vitro studies by Coburn and Kapp³ showed a quantitative relationship between an increased speed of sedimentation and amounts of added fibrinogen or globulin. Gray and Mitchell⁴ confirmed this observation, using protein fractions prepared electrophoretically by the Tiselius method, and observed that the addition of purified albumin reduced the speed of sedimentation. That both anemia⁵ and increased temperature, in vitro,⁶ will change sedimentation rate is well recognized.

Of additional importance are the studies of Hinselmann,⁷ Linzenmeier,⁸ and Krogh,⁹ who reported "stasis" within the fingernail capillaries of normally pregnant and toxemic patients, "stasis" being more pronounced in the latter. More recently, Knisely and co-workers¹⁰⁻¹⁴ have made comprehensive studies of intravascular changes under normal, experimental, and pathologic states. According to them, the findings in normal unanesthetized men and women consist of: an absence of intravascular agglutinations of red blood cells or adherence of white cells to vessel walls, presence of a "laminated" or "streamlined" flow, absence of a plasma "leak" through small vessel walls, and a rate of flow fast enough so that individual red cells cannot be recognized at 48 to 90 diameters of magnification. Contrawise, in various experimental and pathologic states, microscopic agglutinations of blood cells occur within venules and arterioles, and this tendency to form intravascular cell masses causes the blood to circulate, in certain instances, as a thick "sludge." It has been further shown that the state of the circulating blood, as based upon conjunctival observations, is a statistically valid sample of the circulating blood throughout the entire body.

The purposes of this paper are (1) to report the presence of "sludged blood" in women during both normal uncomplicated pregnancy and during pathologic pregnancies, (2) to report that the masses of agglutinated red cells are larger in certain of the pathologic conditions examined than in the uncomplicated pregnancies, (3) to point out probable relationships between (a) the

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alone or in combinations with the steroid hormones. The sarcomatous inducing effect of subcutaneously administered benzpyrene was not influenced by the simultaneously administered steroids. Transplantation of the benzpyrene induced sarcomas appeared to be influenced by administration of hormones. Animals receiving estradiol exhibited sarcomas smaller in size than those observed in the control animals. On the other hand, progesterone, testosterone and desoxycorticosterone acetate appeared to enhance the growth of the transplanted sarcomas. Data is also presented on the effect of steroid substances on the production of neoplastic changes in the endocrine glands and accessory reproductive organs of the rat.

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TABLE I. NONPREGNANT CONTROLS

| PATIENT | PLASMA PROTEINS MG./100 C.C. | | | | | SEDIMENTATION RATE MM./HR. | | | | | SLUDGE | | | |
|----------|---------------------------------|-----------------|---------------|--------------|------|-------------------------------------|---------------------------|-----------------|------------------|--|---------|-------------|-------|-----------------|
| | TOTAL SERUM PROTEIN | FIBRINO- GEN | GLOBU- LIN | ALBU- MIN | A/G | WESTER- GREN CALCU- LATION | UNCOR- RECTED VALUE | HEMATO- CRIT | PLASS- ROURKE | | VENULES | | | ARTERI- OLES |
| | | | | | | | | | | | FINE | MEDI- UM | LARGE | |
| P. R. | 6.7 | 0.28 | 2.3 | 4.4 | 1.9 | 2 | 10 | 41 | 0.17 | | | | | |
| V. E. | 7.5 | 0.22 | 3.1 | 4.4 | 2.4 | 6 | 7 | 41 | 0.12 | | | | | |
| R. L. | 6.9 | 0.31 | 3.0 | 3.9 | 1.3 | 13 | 20 | 44 | 0.36 | | | | | |
| H. H. | 7.4 | 0.34 | 3.1 | 4.2 | 1.4 | 15 | 17 | 46 | 0.37 | | | | | |
| M. O. | 6.7 | 0.38 | 3.2 | 3.5 | 1.1 | 20 | 24 | 45 | 0.43 | | | | | |
| L. W. | 5.8 | 0.30 | 3.2 | 2.6 | 0.82 | 21 | - | - | - | | | | | |
| Average: | 6.8 | 0.30 | 3.0 | 3.8 | 1.5 | 14.5 | 15.6 | 43 | 0.29 | | | | | |
| 379352 | 6.3 | 0.73 | 3.2 | 3.1 | 0.91 | 46 | 59 | 34 | 0.89 | | +++ | +++ | +++ | + |
| 340038 | 6.4 | 0.89 | - | 4.9 | - | 67 | 56 | 35 | 0.86 | | +++ | +++ | +++ | + |

intravascular agglutinations of the blood, (b) the increased in vitro sedimentation rates of blood from these patients, and (c) changes in the concentrations of certain plasma protein fractions.

Material

A total of 52 pregnant and nonpregnant subjects were selected for study. These included 21 whose pregnancy was normal and 23 whose pregnancy was complicated, 16 with toxemia, four with thrombophlebitis and infection, two with acute hemorrhagic shock, and one with ectopic pregnancy. Nonpregnant controls numbered eight.

Equipment consisted of a Leitz dissecting microscope of 48 diameters magnification mounted on a colposcope stand and a Shahan ophthalmic lamp with usual adjustments.

Method

Patients were observed in the supine position from the right side, the light beam being directed through the lateral aspect of the right palpebral fissure. By elevating the right upper lid, with the examiner's left hand, and instructing the patient to deviate vision toward the left, it was possible to focus the Leitz instrument on the lateral bulbar conjunctiva with the right hand. The size of intravascular masses and the degree in reduction of rate of flow were evaluated in fine, medium, and large venules and in arterioles. This was arbitrarily designated as +, ++, +++, or +++, and, on the basis of these direct microscopic observations, an estimate was made of the sedimentation rate. Venous blood was then obtained, without stasis, and collected in tubes for analysis. Sedimentation rates were read in a Wintrobe tube on heparinized blood at ten-minute intervals for one hour, the cell volume being obtained from the same tube after centrifugation for the Plass-Rourke¹⁵ corrected rate. Precautions to maintain constant room temperatures and erect sedimentation tubes were observed during all readings.

Fibrinogen and total serum proteins were determined on the interferometer by a method described by Dieckmann.¹⁶ Albumin and globulin fractionization was obtained by a method described by Pellemer and Hutchinson,¹⁷ which gives results closely approximating those obtained by the Tiselius electrophoretic procedure.¹⁷

Results

1. Observations by Microscopy.—

These numbered 103, seventy-seven of which are tabulated with simultaneously obtained sedimentation rates and plasma protein values (Tables I, II, III, and IV).

a. *Nonpregnant controls:* In none of six female subjects studied whose sedimentation rates were below 24 mm./hour was any intravascular agglutination of the blood observed. Occasionally, a "laminated flow," as described by Knisely and associates,¹⁴ was seen in the large venules of some eyes. However, two other patients, whose diagnoses were pelvic inflammatory disease and generalized carcinomatosis, had large, easily observable agglutinations within venules and arterioles, a reduced rate of blood flow, and, in some vessels, temporary cessation of flow; and, as anticipated, their sedimentation rates were high (Table I).

b. *Normal pregnancy:* "Sludged blood," consisting of intravascular agglutinations of erythrocytes and reduced rates of flow with temporary cessation (of flow) in some vessels, was observed in all subjects with sedimentation rates of 33 mm./hour or more. "Sludge" was more easily seen in those patients

with an increased sedimentation rate. In fact, it seemed that the size of the cell aggregates increased progressively in direct ratio with the hourly uncorrected sedimentation rate. "Sludge" was detected most readily in fine venules, where it had the appearance of a string of beads; next in medium-sized venules, where it had the appearance of granules; and least readily in large venules, appearing there as larger clumps. "Sludge" was not observed in arterioles during normal pregnancy, almost certainly because the masses were small and the blood flow very rapid. The largest cell masses, and the greatest reduction in rates of flow, were seen in those patients who were near term, in labor, or early in the puerperium (Table II).

c. Pathologic pregnancy; -pregnancy toxemia: A noticeable narrowing of arterioles could be detected in most patients. In addition, intravascular agglutinations and reduced flow rates were observed. The sizes of masses comprising the "sludge" were larger, the rate of flow considerably more decreased, and cessation of flow more prolonged, as compared with normal pregnancy. One patient (M. L. 323886) deserves special comment. This Case, POG1, unregistered, and six and one-half months pregnant, was admitted in coma with a history of one convulsion. Immediately after the third convulsion, observations disclosed arteriole constriction. The venules, in certain areas, were segmentally constricted in such a way that short segments contained blood and intervening portions were empty. Blood flow through these vessels had ceased, and was not reestablished for several minutes. In larger venules the blood flow appeared to be very slow although no agglutinations could be detected.* During the two hours following sedation and intravenous hypertonic solutions the constricted vessels dilated, flow through them was re-established, and individual agglutinations could be detected. The hematocrit reading changed from 50 per cent, immediately after the third convulsion, to 45 per cent two hours later, and subsequently to 37 per cent some time afterward. The sedimentation rates during this period were 15 mm. (immediately after a convulsion), and 38, 43, 31, and 39 mm./hour during subsequent treatment. No other convulsions occurred. Delivery followed premature artificial rupture of the membranes and the administration of solution of posterior pituitary. The puerperium was uncomplicated. Observations of the sedimentation rate conducted on a second eclamptic (L. E. 379384) showed similar changes. The rates in this case were 32 mm. (immediately after a convulsion), and 45 and 47 mm. during and after treatment; the hematocrit was 38, 35, and 31 per cent, respectively (Table III).

Thrombophlebitis and infection: Microscopic conjunctival examination disclosed large intravascular agglutinations within fine, medium, and large venules and in arterioles. In addition, stasis¹⁹ and a few minute thrombosed venules were seen. Sedimentation rates were unusually high in these patients.

Hemorrhagic shock: Three instances of severe hemorrhagic shock were observed, two in the same patient. The first (E.W. 376643), P4G5, aged 42 years, was admitted at thirty-eight weeks in shock of two hours' duration from severe hemorrhage due to placenta previa. Distinct, irregular, rigid agglutinations were observed within venules of the conjunctiva. These masses moved slowly, and reversal of flow for short intervals was frequent. Agglutinations were visible also in arterioles, and the rate of flow in them was slowed. Following transfusion of 4,200 ml. of blood the patient's condition improved, and there was no visible "sludge." However, two hours after a cesarean hysterectomy the "sludge" again became visible and the sedimentation rate became elevated. The patient was discharged well on the sixtieth postoperative day, the puer-

*Knisely and Bloch²⁰ have observed similar concentration in one eclamptic patient, and they interpret absence of visible agglutination to vessel leak which packs the masses tightly together so that edges of individual masses cannot be seen.

TABLE II. NORMAL PREGNANCY

| OBSERVATIONS | PLASMA PROTEINS MG./100 C.C. | | | | | SEDIMENTATION RATE MM./HR. | | | | SLUDGE | | | |
|--------------|---------------------------------|-----------------|---------------|--------------|-------------|-------------------------------------|---------------------------|-----------------|------------------|---------|-------------|-------|-----------------|
| | TOTAL SERUM PROTEIN | FIBRINO- GEN | GLOBU- LIN | ALBU- MIN | A/G | WESTER- GREN CALCU- LATION | UNCOR- RECTED VALUE | HEMATO- CRIT | PLASS- ROURKE | VENULES | | | ARTERI- OLES |
| | | | | | | | | | | FINE | MEDI- UM | LARGE | |
| 9 | 5.3-6.5 | 0.27- 0.43 | 2.3- 2.8 | 3.0- 3.8 | 0.9- 1.7 | 9-32 | 11-34 | 31-44 | 0.20- 0.57 | | | | |
| Average: | 5.94 | 0.34 | 2.6 | 3.3 | 1.3 | 18 | 22 | 37 | 0.34 | | | | |
| 5 | 5.0-6.8 | 0.34- 0.50 | 1.8- 3.2 | 2.9- 3.6 | 1.0- 1.7 | 15-43 | 26-42 | 30-39 | 0.59- 0.63 | + | + | | |
| Average | 5.74 | 0.42 | 2.4 | 2.7 | 1.4 | 28 | 37 | 35 | 0.61 | + | + | + | |
| 7 | 5.4-6.9 | 0.33- 0.64 | 2.4- 3.4 | 2.8- 3.7 | 0.9- 1.5 | 12-46 | 32-50 | 31-40 | 0.53- 0.73 | + | + | + | + |
| Average: | 6.2 | 0.44 | 2.8 | 3.3 | 1.2 | 29 | 41 | 38 | 0.66 | + | + | + | + |

TABLE IV. PATHOLOGIC PREGNANCY

| PATIENT | PLASMA PROTEINS MG./100 C.C. | | | | | SEDIMENTATION RATE MM./HR. | | | | | SLUDGE | | | |
|---------------------------------------|---------------------------------|----------------------|-------------------|-------------------|-------------------|----------------------------------|---------------------------|-----------------|-------------------------------------|---------|-------------|-------|-----------------|----|
| | TOTAL SERUM PROTEIN | FIBRINO- GEN | GLOBU- LIN | ALBU- MIN | A/G | WESTER- GREN CAL- CULATION | UNCOR- RECTED VALUE | HEMATO- CRIT | PLASS- ROURKE CORREC- TION | VENULES | | | ARTERI- OLES | |
| | | | | | | | | | | FINE | MEDI- UM | LARGE | | |
| <i>Shock and Hemorrhage</i> | | | | | | | | | | | | | | |
| E. W. 376643 | 5.6 | 0.53 | 3.1 | 2.5 | 0.8 | 53 | 52 | 38 | 0.84 | +++ | +++ | +++ | +++ | |
| A. B. 124582 | 5.6 4.8 5.5 | 0.25 0.23 0.31 | 2.4 2.1 2.7 | 3.2 2.7 2.8 | 1.3 1.3 1.0 | 5 4 18 | 24 29 51 | 31 35 36 | 0.35 0.44 0.80 | | | | | + |
| <i>Thrombophlebitis and Infection</i> | | | | | | | | | | | | | | |
| E. W. 376643 | 5.3 | 0.52 | 2.9 | 2.5 | 0.9 | 48 | 62 | 31 | 0.90 | +++ | +++ | +++ | +++ | ++ |
| G. F. 385319 | 6.3 | 1.25 | 4.2 | 2.1 | 0.5 | 164 | 56 | 37 | 0.89 | +++ | +++ | +++ | +++ | ++ |
| G. G. 164236 | 6.3 | 0.49 | 2.8 | 3.5 | 1.3 | 39 | 44 | 38 | 0.71 | ++ | ++ | | + | |
| A. W. 377805 | 6.8 | 0.28 | 3.7 | 3.1 | 0.8 | 18 | 57 | 32 | 0.84 | +++ | +++ | +++ | +++ | + |
| <i>Ectopic Pregnancy</i> | | | | | | | | | | | | | | |
| E. G. 385385 | 5.9 | 0.37 | 1.9 | 3.9 | 2.0 | 15 | 16 | 44 | 0.30 | | | | | |

tion rates from patients with pregnancy toxemia tended to be higher than those obtained during normal pregnancy. There was close correlation with plasma fibrinogen values, less with albumin, globulin, or A:G ratio, and no relationship with total serum proteins (Figs. 1, 2, and 3). The Plass-Rourke corrected rates (computed on the percentage of hourly sedimentation as related with the hematocrit reading) related to plasma fibrinogen figures (Fig. 4). The Westgren calculation for sedimentation rate, computed from plasma protein fractions by the formula, $\text{Sedimentation Rate} = 140.4 \text{ fibrin. \%} + 6.22 \text{ glob. \%} + 6.09 \text{ alb. \%} - 25.5$, yielded inconsistent results.

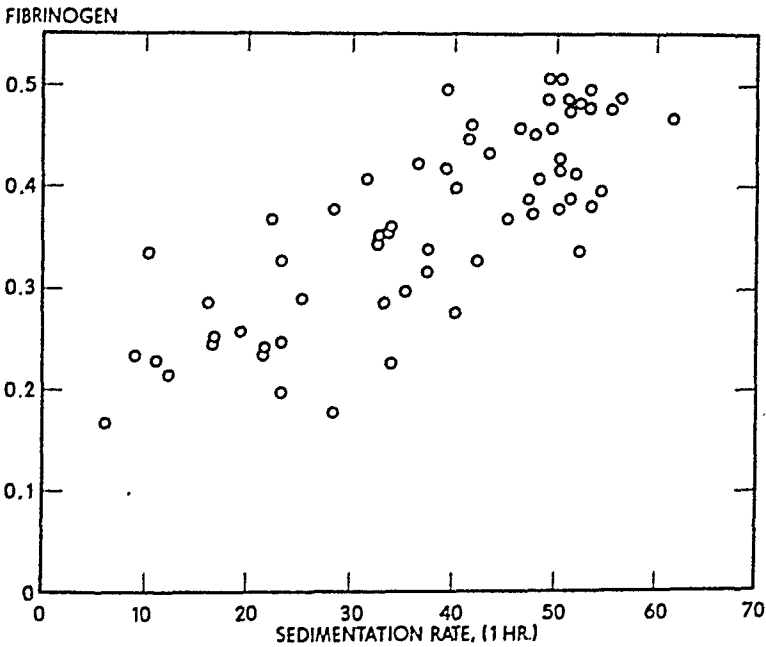


Fig. 1.—Erythrocyte sedimentation rate, sludged blood, and plasma proteins during pregnancy. Fibrinogen and sedimentation rate.

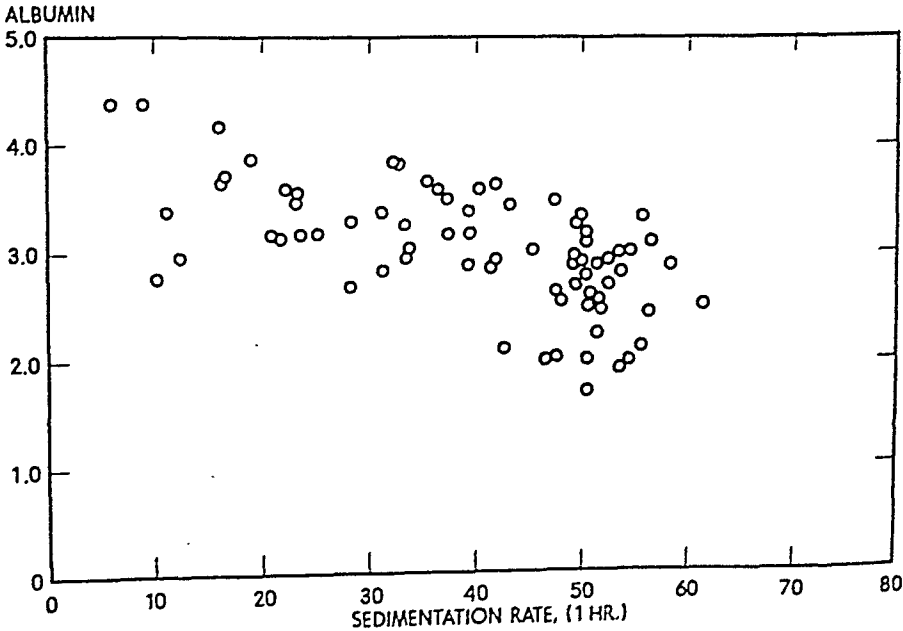


Fig. 2.—Erythrocyte sedimentation rate, sludged blood, and plasma proteins during pregnancy. Plasma albumin and sedimentation rate.

perium being complicated by a pelvic thrombophlebitis. The second case (A. B. 124582), P9G12, aged 37 years, was admitted at twenty weeks gestation for therapeutic abortion because of hypertensive vascular disease. An estimated 1,500 ml. hemorrhage occurred during dilation and curettage. Microscopic examination commenced during the operation disclosed large intravascular masses of red cells, and markedly reduced rates of flow in all small venules. Transfusions of whole blood (1,500 ml.) restored blood volume and an intra-uterine pack controlled hemorrhage. Two days later a second hemorrhage followed removal of the uterine pack. Profound shock resulted. Microscopic examination disclosed constricted veins but no visible "sludge," and the sedimentation rate was only 24 mm./hour. However, following transfusion of whole blood and curettage, intravascular agglutinations and visible reduction in rate of flow occurred; the sedimentation rate became 51 mm./hour. The remainder of the hospital stay was uncomplicated.

Ectopic pregnancy: One patient (E. G. 385385) was observed who had a provisional diagnosis of acute pelvic inflammatory disease. This case had no visible "sludge" and a low erythrocyte sedimentation rate. An ectopic pregnancy with left hematosalpinx was discovered during laparotomy (Table IV).

2. Sedimentation rate.—

Estimates of sedimentation rate, based on conjunctival observations, closely approximated the measured, uncorrected, hourly values (Table V). In addition, microscopic findings as to the size of the masses correlated with a sliding scale of sedimentation rates (Table VI). Values were higher at term, in labor, or during the puerperium, and highest in infections. In addition, the sedimenta-

TABLE V. RELATIONSHIP OF E.S.R. TO AMOUNT OF INTRAVASCULAR "SLUDGE"

| PATIENT | SEDIMENTATION RATE 1 HOUR | VENULES | | | ARTERIOLES |
|--------------|---------------------------------|---------|--------|-------|------------|
| | | SMALL | MEDIUM | LARGE | |
| 7 controls* | 7-20 | | | | |
| 379352 | 59 | +++ | +++ | +++ | + |
| 340038 | 56 | +++ | +++ | +++ | + |
| M. M. 21296 | 23 | + | | | |
| I. N. 381922 | 24 | + | + | | |
| S. L. 124582 | 24 | | | | |
| A. B. 383217 | 26 | + | + | | |
| E. L. 271273 | 29 | | | | |
| S. L. 124582 | 29 | | | | |
| G. B. 357426 | 32 | ++ | + | + | |
| M. V. 388369 | 34 | ++ | + | + | |
| M. C. 158661 | 38 | + | + | | |
| M. T. 378782 | 40 | +++ | + | | |
| E. R. 375466 | 43 | +++ | ++ | ++ | |
| M. V. 388369 | 48 | +++ | +++ | +++ | |
| G. L. 375409 | 48 | +++ | +++ | ++ | + |
| A. S. 376640 | 50 | +++ | +++ | ++ | |
| R. R. 381772 | 51 | +++ | ++ | ++ | |
| R. R. 381772 | 51 | +++ | +++ | ++ | |
| M. R. 376091 | 51 | +++ | +++ | ++ | + |
| M. R. 376091 | 51 | +++ | +++ | ++ | + |
| S. L. 124582 | 51 | ++++ | ++++ | +++ | + |
| A. S. 376640 | 53 | +++ | +++ | ++ | |
| M. V. 388369 | 54 | +++ | +++ | ++ | |
| M. F. 378732 | 55 | +++ | +++ | ++ | |
| M. F. 385319 | 56 | +++ | +++ | +++ | ++ |
| M. M. 193700 | 57 | +++ | +++ | ++ | + |
| M. W. 376643 | 62 | ++++ | ++++ | +++ | ++ |

*Nonpregnant controls.

TABLE VI. RELATIONSHIP OF E.S.R. TO THE ESTIMATED VALUE

| NUMBER PATIENTS | AVERAGE SEDIMENTATION RATE 1 HOUR | ESTIMATED VALUE |
|-----------------|---|-----------------|
| | | |
| 12 | 17 | below 20 |
| 5 | 24 | 20-30 |
| 4 | 42 | 30-40 |
| 5 | 49 | 35-45 |
| 6 | 42 | 40-50 |
| 3 | 53 | 45-55 |
| 7 | 51 | 50-60 |
| 4 | 53 | 55-65 |
| 1 | 62 | 60-70 |

Knisely-Bloch technique for intravascular observations in the human being, as used in this study, offers much improvement over the previously used methods since an uninterrupted, clear, and detailed examination of entire vessel segments and surrounding tissue spaces can be easily obtained.

It would seem that intravascular "sludge" was related to rouleaux formation, a phenomenon already associated with the erythrocyte sedimentation rate.¹ Rouleaux formation was originally attributed to an attraction between negatively and positively charged erythrocytes,^{21, 22} but more recent investigations suggest cell stickiness or cohesiveness as an important mechanism. Just what constitutes stickiness between cells is not well understood. According to Ponder,²³ intercellular cohesiveness is probably a property of surface tension. Lecompte Du Nouy²⁴ studied the later phenomena extensively and concluded that larger protein molecules in solutions tend to concentrate at interfaces (as monolayers), thus producing a more viscous substance. Knisely, and associates,¹³ while studying sludged blood, observed and photographed under darkfield illumination in vitro a thick, glassy, cottony precipitate (probably a protein) present between and around all the red cells of each agglutinated clump.

It should be stressed, however, that rouleaux formation differs, by definition, from an intravascular agglutination of cells (or "sludge"). The former consists of an in vitro piling-up of red cells, like coins, one on another; the latter of in vivo intravascular cell aggregates wherein erythrocytes are held together at all angles to each other.¹⁴ Nevertheless, it would appear that both phenomena relate to an increased cellular cohesiveness, and the nature of the substance causing this should become an object for much research.

The addition of hyaluronic acid, a tissue polysaccharide, to citrated blood will increase sedimentation and rouleaux, while hyaluronidase, a tissue enzyme, has a reverse effect. However, the addition of either desoxyribonucleic acid, gelatin, fibrinogen, or hyaluronic acid to normal citrated blood causes a considerably increased erythrocyte sedimentation. And Meyer and co-workers²⁵ suggest that probably all highly asymmetrical molecules of large size will increase sedimentation. It would seem that the basic problem concerning "sludged blood" does not consist in finding artificial methods of producing it in vitro as rouleaux. The problem is more that of altering "sludge" in the living animal.

In the experimental animal "sludged" blood follows trauma. In fact, photographs¹⁴ of minutely injured areas on monkey omentums reveal intra-

Comment

This study correlates the presence of intravascular agglutinations of erythrocytes and reduced rates of blood flow during pregnancy with the erythrocyte sedimentation rate, and the latter with plasma fibrinogen and albumin levels. Both Fähreus²⁶ and Linzenmeier⁸ suggested such a relationship, their observations being based upon opthalmoscopic examinations of the retina, upon fingernail microscopy, and upon artificially produced stasis in extremities. However, the

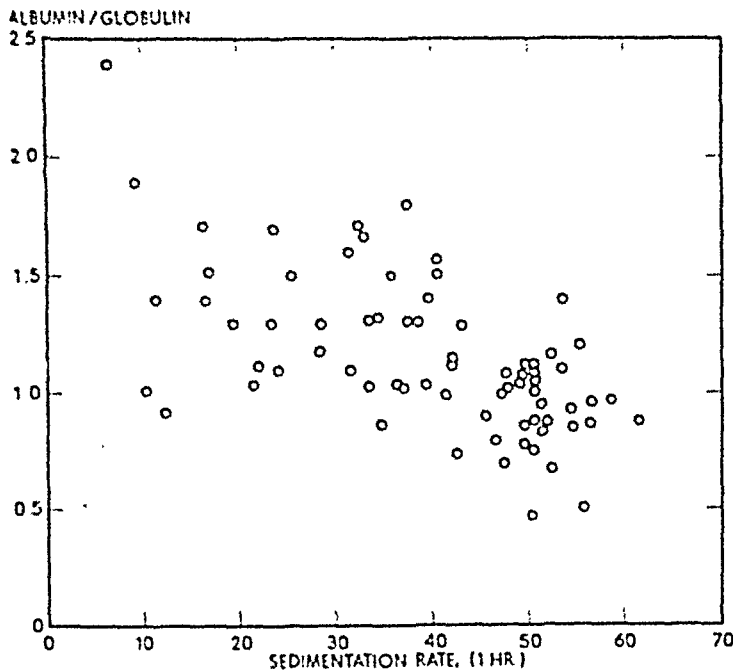


Fig. 3.—Erythrocyte sedimentation rate, sludged blood, and plasma proteins during pregnancy. Albumin globulin and erythrocyte sedimentation rate.

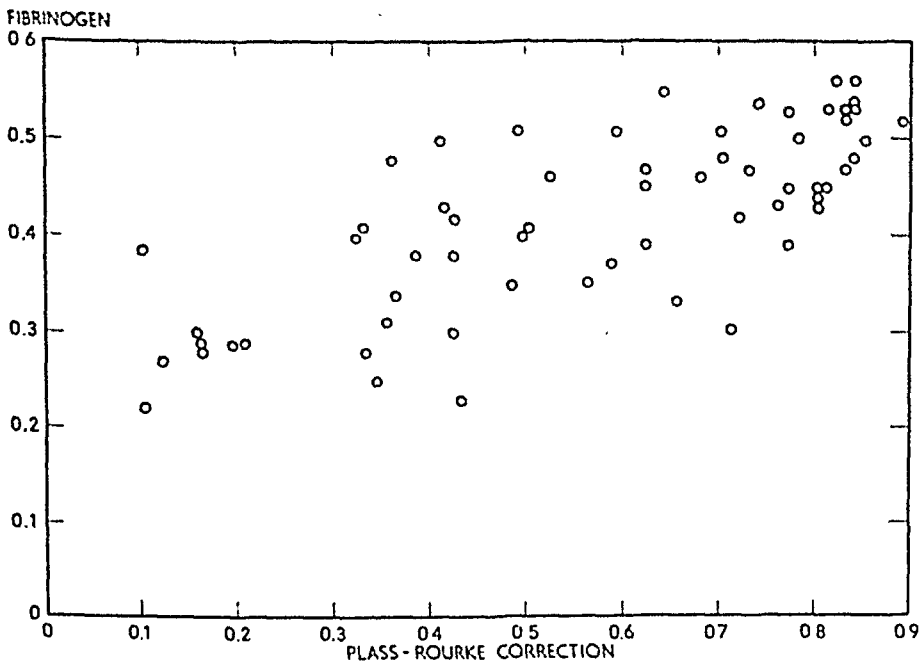


Fig. 4.—Erythrocyte sedimentation rate, sludged blood, and plasma proteins during pregnancy. Fibrinogen and Plass-Rourke correction.

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Discussion

DR. M. H. KNISELY.—Some new terms have been used here. "Sludged blood" is not yet in common use in medicine. Dr. Edward H. Bloch and I worked at the University of Tennessee College of Medicine in Memphis with Drs. Stratman-Thomas and Eliot for two years studying sludged blood in monkeys infected with knowlesi malaria. Later we found intravascular agglutination of the blood of human beings diagnosed by practicing physicians as having about 40 pathologic conditions and diseases. (Cf. Knisely, Stratman-Thomas, Eliot and Bloch, 1945; and Knisely and Bloch, 1942, 1945). Further, when working with Dr. Lathan Crandall and his colleagues in Memphis we found precipitation and agglutination of the blood of traumatized dogs, and working with Dr. Lester Dragstedt, Dr. Franklyn Brooks and Louise Warner we have found agglutination of the blood of animals and people following burns. In the laboratory we have been interested in finding the kinds of damage caused by the precipitation and/or agglutination of the circulating blood to a circulating sludge.

Words and sentences do not clearly tell what we mean by "sludging of the blood." Hence, at this point I would like to show a short motion picture taken through the microscope which shows the course of some of the events in traumatic shock. I think that what it shows is closely related to the changes in the blood which Dr. Odell and colleagues have found following separation of the placenta. (The motion picture was presented; it showed that in traumatized tissue the blood flowing through the traumatized areas changes from a fluid to a stiffly precipitated and agglutinated sludge [Cf. Knisely, Eliot and Bloch] 1945.) When this process has been going on in large enough areas of tissue for a long enough time, all of the circulating blood is changed to a stiff mucklike sludge. After the blood is changed to a sludge the masses of which the sludge is composed resist passage through the long cone-shaped arterioles, capillaries, and postcapillary venules. In consequence, the rates of flow

vascular masses forming the instant circulating blood contacts crushed tissues. Conversely, bleeding experiments, conducted within limits of safety on human beings, did not cause the formation of sludge within the first half hour.²⁶ The two instances of hemorrhagic shock in this report substantiate these observations. In the first case (E. W. 376643) hemorrhagic shock had existed for two hours prior to hospitalization, sufficient elapsed time for considerable hemodilution and, as a result, an elevated sedimentation rate (because of anemia), and an increased rouleaux and "sludge." However, in subsequent examination of this patient, as well as of the other patient in hemorrhagic shock (A. B. 124582), it is significant that operative trauma preceded the appearance of intravascular "sludge."

Gray and Warner²⁸ have produced and photographed "sludged" blood in guinea pigs by injecting electrophoretically prepared beef fibrinogen, and Dieckmann²⁷ has observed a temporary alleviation of "stasis" within fingernail capillaries following intravenous hypertonic glucose solution. In the present study two patients received intravenously 25 and 60 Gm., respectively, of electrophoretically purified albumin. There was a transitory decrease in the amount of "sludge" and speed of sedimentation. In addition, the effect of intravenous 5 per cent saline solution and human plasma was studied. And two patients were observed under dicumerol medication. None of these altered permanently this "sludge" or the sedimentation rate to a significant degree.

In two eclamptics hemoconcentration was associated with a lowered sedimentation rate. This observation agrees with those²⁹ who suggest that the removal of plasma in vitro interferes with rouleaux formation, so that rouleaux becomes smaller and sedimentation rate slower. In addition, the consistently increased "sludge" in pre-eclamptic toxemia, as compared with normal pregnancy, and the obvious plasma "leak" in convulsive toxemias, suggests that circulatory physiology sometimes becomes sufficiently disturbed in the former to the point of anoxia, and in the latter results in the loss of plasma to the tissues; in short, a cause and effect relationship. Such a sequence of events occurs experimentally, at least, with "sludged blood."^{12, 14}

Summary

"Sludged" blood, as characterized by intravascular agglutinations and reduced rate of flow, is found in normal and pathologic pregnancy and in some nonpregnant women. This phenomena is apparently related to an increased erythrocyte sedimentation rate which, in turn, correlates with plasma fibrinogen and albumin values. It is possible to make estimates of erythrocyte sedimentation rate from the microscopic conjunctival observations.

During shock "sludge" is apparently related to subsequent hemodilution or to the accompanying operative trauma, rather than to an acute loss of blood. During thrombophlebitis and infections the size of intravascular masses is particularly increased. During preconvulsive toxemias "sludge" is increased, and during eclampsia anoxia could explain the rapid loss of plasma to the tissues.

The authors are indebted to Dr. Wm. J. Dieckmann, Dr. M. M. Knisely, and Dr. E. H. Bloch for advice concerning this study.

ductions of the work of Linzenmeier and of the only other man in the United States who had done that work, namely Friedlander of Detroit. We were able to convince ourselves that the sedimentation rate was exactly what it was held out to be, namely, a delicate test for certain clinical conditions such as infections, degenerative diseases, and malignancies. We were able to satisfy ourselves that as compared with sedimentation in normal people, these other conditions hastened the settling of the red cells. It took us a considerable period to convince our colleagues in our department of gynecology and obstetrics that the sedimentation rate was a proper adjunct in the study of the patient, even though we were able to demonstrate that it was a somewhat more delicate prognostic as well as diagnostic test than the ordinary leucocyte count which up to that time has been the sole laboratory criterion. It took ten years before clinicians in other branches of medicine paid any attention to the sedimentation rate, namely, those in the field of tuberculosis, the pediatricians, and finally the internists. Now the sedimentation rate is a definitely accepted part of the procedure in the study of such patients.

A quarter of a century ago our facilities consisted of an ordinary microscope, a very low power objective, and a miniature light source. The finger of the patient was mounted on a tongue depressor and held with adhesive. A drop of immersion oil was placed over the clean nailbed. The light was obtained with a cystoscope bulb and the current provided by a dry cell battery. Even with that primitive set-up we were able to see some of the things which everyone should see, the terminal capillary loops with efferent and afferent arms. It was entirely possible to see the erythrocytes moving through these loops. In the healthy individual these loops are as regular as a palisade fence, whereas in chronic cardiac disease, chronic nephritis, and other types of circulatory disturbances, there are changes which result in all sort of distortions many of which were named in the literature of that day. In the severe toxemias we thought we were able to demonstrate angiospasm, which was of some clinical significance.

The correlation of the sedimentation rate with studies in capillary microscopy and the work presented here has advanced so far beyond these early studies that it demonstrates conclusively that the clinician cannot carry out such fundamental studies, yet cannot carry on the practice of medicine without this kind of study. It is gratifying to see that the talents of biochemists, of physiologists, and of anatomists are being applied to this field of medicine which I think is exceedingly important and with which every one of you can make himself at least basically familiar by looking at your own or someone else's fingernail bed.

Finally, may I say that the original use for the sedimentation rate of Linzenmeier was in gynecology. Today, I think it is generally agreed that in practice and not necessarily in precise physiologic and biochemical laboratory, the best outfit for the study of the sedimentation rate is the Landau-Adams microsedimentation technique which is exceedingly simple and quite accurate, even when compared to the Westergren method.

DR. ODELL (Closing).—Our interest in the phenomena of "sludged blood" stems from the possibility that it might explain certain functional disturbances in pregnant patients, particularly in toxemias of pregnancy. The occurrence of edema and proteinuria in toxemia patients has never been well understood. And the circulation of clumped erythrocytes through the vascular system might interfere with normal metabolic exchange. We have noted particularly large intravascular agglutinations, and markedly elevated sedimentation rates in those toxemia patients with a pronounced proteinuria.

through tissues become too slow, the tissues become anoxic, and the endothelium of the postcapillary venules becomes anoxic, and in consequence begins to leak, letting fluid out through the vessel walls into the tissues. The stagnant anoxia of the vessel walls (a) permits loss of fluid into the tissues, (b) causes hemoconcentration of the circulating blood, and (c) causes decreasing circulating blood volume. The film showed visible aspects of the above). This film is not a finished motion picture ready for public distribution; it is an assembly of laboratory records pieced together to demonstrate these processes until we have time to make a long careful cinema record of all the stages of these processes as we have observed them in experimental traumatic shock.

With any given arterial pressure, venous pressure, and degree of dilatation of arterioles, capillaries, and venules, the degree of reduction of the rates of flow through capillaries caused by sludging of the blood is proportional to a combination of two mechanical factors: (1) the sizes of the masses of agglutinated blood cells, and (2) the internal rigidities of these masses. The larger and more rigid the more they resist passage through small vessels, particularly the long, narrow, cone-shaped arterioles, and thus reduce the rates of flow of blood through the capillary networks of all tissues. Thus the changing of the blood to a sludge can, depending upon the mechanical consistency of the sludge, cause many different degrees of slowed flow, endothelial anoxia, leaking of vessels, hemoconcentration, and reduced venous return. Accumulating laboratory evidence indicates clearly that when the masses become large and rigid enough this series of mechanisms becomes the direct cause of death (Cf. Knisely, Stratman-Thomas, Eliot, and Bloch, 1945).

One other pathologic consequence of changing the blood to a sludge is a little more complicated, and takes a little more time to present. When India ink is injected into a frog, each particle of the ink receives a coating of a glassy precipitate, probably protein derived from the blood plasma. This coating material acts as an opsonin; it sticks to and then is instantly ingested (with its contained ink) by the phagocytic lining cells of the liver sinusoids. In monkeys with malaria the red cells which are coated by glassy precipitates also stick to the linings of hepatic sinusoids and are instantly ingested, and coated red cells are also phagocytized in the spleen and bone marrow. The rate of phagocytosis of coated red cells can be much higher than anyone might suspect; in one monkey with malaria, in which we determined the rates of phagocytosis by doing consecutive closely spaced parasite counts, we found that the animal phagocytized one-third of all his circulating blood in three hours. It seems probable that in this monkey all the conditions necessary for ingestion of coated red cells were optimal, thus giving very high rates of phagocytosis. But it is important to know that one major effect which can follow agglutination of the blood is the rapid phagocytic destruction of coated circulating blood cells, and that the rate of phagocytosis of coated red cells can be so rapid as to cause an anemia and/or a decrease in the animal's circulating blood volume. In response to the decreased blood volume, the arterioles of many tissues are shut off for much longer periods than they are during normal phases of normal physiology. It seems quite probable that this series of mechanisms may be occurring in many human pathologic conditions and diseases. It is of course now necessary to find out whether all the different kinds of coatings on red cells which can stick them together in agglutinated masses are equally phagocytozable, or to find out the conditions under which each kind of coating is phagocytizable.

Often in animals the tendency of anoxic, leaking vessels to cause a hemoconcentration is counterbalanced by the tendency of the phagocytosis of coated red cells to cause reduced red-cell counts. As fluid and red cells are both being lost, the red-cell count of the circulating blood stays normal while, insidiously, these factors both contribute to reduction of blood volume, venous pressure, and venous return (Cf. Knisely, Stratman-Thomas, Eliot and Bloch, 1945).

DR. JOSEPH L. BAER.—The subject matter of the main paper is distinctly over my head. It happens that a quarter of a century ago I was interested, and Dr. Reis with me, in both sedimentation rates and capillary microscopy. We labored long hours at Michael Reese Hospital studying sedimentation rates and developing what we felt were fairly good repro-

The hypothesis that vitamin B complex deficiency prevents the liver from inactivating estrogens is based on experimental work by M. S. and G. R. Biskind.^{8, 9} Castrate animals with pellets of estrogen implanted into the spleen showed no estrogenic stimulation of the vaginal mucosa. After a period on a vitamin B complex free diet, however, the animals lost weight and the liver lost its ability to inactivate estrogens, since their vaginas showed constant estrogenic stimulation. Similar results were obtained by Shipley and Gyorgy.⁴² Supportive data were furnished by Segaloff and Segaloff,³⁹ and others.⁴³ M. S. Biskind and Shelesnyak¹⁰ have also reported that under similar conditions of vitamin B deprivation, the liver was unable to inactivate endogenous estrogen from ovarian tissue resident in the spleen.

In 1943 M. S. Biskind¹¹ claimed that the hypothesis also applied to the human being.

"Evidence is presented that menorrhagia, metrorrhagia, cystic mastitis, premenstrual tension, and possibly other syndromes related to an excess of estrogen are caused by a failure of the liver to inactivate estrogen because of deficiency of the vitamin B complex. Administration of the B complex in adequate dosage orally, parenterally, or by both routes, led to prompt improvement in these conditions."

This quotation represents the summary in toto from this article.

The evidence for these statements was derived from twenty-nine patients, of whom seven were discussed in detail. Atrophic glossitis, cheilosis, stomatitis, neuritic pains, or a combination of these symptoms was considered the evidence of vitamin B complex deficiency. The height and weight were noted in four of the seven cases, the average being only 5 feet, 2½ inches in height, but 160.25 pounds in weight. In the discussion the author states that most of the twenty-nine patients were overweight. Two of the early symptoms of the vitamin B complex deficiency are anorexia and loss of weight.^{19, 44, 45} It is, therefore, unlikely that the obese patients at least were actually deficient.

The state of the endometrium was mentioned in only one patient. The tissue was obtained by curettage and showed hyperplasia of the endometrium. No other evidence was presented that the menorrhagia or metrorrhagia in the patients was actually caused by an excess of estrogen. The assumption that menorrhagia or metrorrhagia is in all cases due to an excess of estrogens is not valid. Such an excess would produce a hyperplasia of the endometrium and thus be easily demonstrable. Various workers have demonstrated that functional bleeding may be associated with endometrial hyperplasia. However, it may also be associated with merely a secretory type of endometrium or even atrophic endometrium. Hoffman studied the endometrium from 128 patients with functional bleeding, 20 to 35 years of age.²⁷ He found hyperplasia of the endometrium in 51 per cent, secretory type in 38 per cent, atrophic in 5 per cent, and early proliferative in 6 per cent. Sturgis Abarbanel, and Nader⁴⁶ found hyperplasia of the endometrium in only 35 per cent of a group of seventeen patients with menometrorrhagia. Hamblen,²³ in a series of 301 patients of all ages with menorrhagia, found "hyperestrogenic" endometrium in 25.6 per cent. This group contained many adolescent and climacteric women. In a group of 129 which included few adolescent or climacteric women, hyperestrogenic endometrium was found in only 11.8 per cent. The figures presented here do not include the endometria classified by Hamblen as "persistent estrogenic." These showed "no active proliferation but instead cytologic and functional evidences of regression." These are not the findings that would be obtained with an excess of estrogen.

In 1944 a second paper on this subject was published jointly by the three Biskinds.¹² The series was "extended to include studies on 104 patients of

VITAMIN B COMPLEX, MENORRHAGIA, AND CANCER

A Critical Review*

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AN INCREASING number of publications have been concerned with the relation of vitamins of the B complex to the metabolism of estrogens in the human being. Deficiency of these vitamins has been assumed to be the indirect cause of various gynecologic disorders. Therapy with vitamin B complex is claimed to have cured these conditions.^{3, 11-13} Insufficient vitamin B complex has also been implicated as a causal factor in the production of uterine carcinoma. This implication naturally has led to the suggestion that vitamins of the B complex might act as a prophylactic against the development of cancer.³ A summary of the original article on vitamin B and carcinogenesis appeared in the editorial section of the *Journal of the American Medical Association*.¹⁵ Widespread publicity resulted when it was discussed in some detail in two issues of a pharmaceutical firm publication sent to every physician.^{1, 2}

Theories on the relation of B complex vitamins to gynecologic disorders and carcinogenesis have been based on an assumption which has recently been proved to be erroneous.¹⁴ For this reason the present authors believe that a critical review of this subject would be of some value.

The hypothesis that vitamin B complex is related to gynecologic disorders and to carcinoma of the uterus may be stated as follows: The liver normally destroys or inactivates the estrogens produced in the body (endogenous estrogens). With insufficient vitamin B complex intake, the liver no longer has this ability or function. An excessive amount of estrogen results, which in turn is the cause of menorrhagia, metrorrhagia, premenstrual tension, and cystic mastitis.¹¹⁻¹³ Acting over long periods of time, the excessive estrogen may also induce uterine cancer.³

It is well established that the liver normally inactivates circulating estrogens or at least changes them to a much less active form. For example, Golden and Sevringhaus²² found that the ovary transplanted to the mesentery of the experimental animal lived and flourished, as did the ovary transplanted to a subcutaneous site. The vagina of these latter animals showed estrogen stimulation. With the mesenteric graft, however, the vagina remained in a constant castrate condition. The venous drainage of the mesentery is directly to the liver via the portal vein. It is believed, therefore, that the liver inactivates the ovarian estrogen before it can reach the general circulation. Several workers have subsequently demonstrated that estrogens implanted as pellets^{6, 7, 29, 30} or injected in solution into the spleen^{36-38, 40} are also inactivated. The venous drainage here also is to the liver. The inactivation was not due to the spleen per se, since the subcutaneously transplanted spleen with a new blood supply draining into the systemic circulation had no inactivating effect. Other in vivo^{35, 41, 47} and in vitro^{17, 24, 25, 28, 34} experiments have also shown that the liver is able to inactivate estrogens.

There is some evidence in the human being that the liver inactivates estrogens.^{4, 5, 16, 20, 21, 32, 48} For example, in cirrhosis of the liver in the male, there may be increased excretion of free estrogens in the urine and an associated gynecomastia.²¹

*Presented before the Chicago Gynecological Society, Dec. 20, 1946.

twice before eliminating a diagnosis of precancerous change if found in a 40-year-old." The third patient was 64 years old and had a typical squamous cell carcinoma of the cervix.

As an addendum to their paper Ayre and Bauld state that of twenty patients suffering from uterine cancer, 90 per cent had a low thiamine excretion coupled with abnormally high endogenous estrogen level, and 20 per cent also showed a deficient excretion of riboflavin. The authors conclude that if their work were confirmed and their theories substantiated, one could detect a potential cancer-producing mechanism even before the cancer develops. A combination of low thiamin and abnormally high endogenous estrogen could be recognized as a dangerous precancerous condition. Recognition of the findings and their dietetic correction would thus prevent the development of cancer.

Ayre and Bauld used the "vaginal and cervical cytological smear" as a quantitative index of endogenous estrogen production. The validity of using this particular method to determine that excessive endogenous estrogens are being produced in a patient has yet to be established. The smear is valuable in differentiating whether the vaginal mucosa is or is not stimulated by estrogens. It may even be considered quantitative in that one can distinguish between a full estrogenic effect (due to optimal amounts of endogenous or administered estrogens) and a partial effect due to less than optimal amounts. The vaginal mucosa (and that of the portio portion of the cervix) responds as much as it is able to optimal amounts of estrogen. This maximal growth response is reflected in the desquamated cells found in the smear. Since the vaginal mucosa is already responding to the greatest of its ability under optimal conditions, there can be no further response to excessive amounts of estrogen. Ayre and Bauld made only the statement that the presence of excessive amounts of estrogens was determined by the "vaginal and cervical cytology smear." No mention was made of their findings in the smear that indicates this excessive estrogen. They did not quote any data of their own or publications of other workers to establish the validity of this method.

Ayre and Bauld attach great significance to the finding of cornified smears from a vaginal mucosa of the functional type in postmenopausal women with uterine cancer. However, McLaren³¹ has demonstrated both by smear and by biopsy that functional type cornified vaginal mucosa may be found in at least 65 per cent of normal postmenopausal women. This figure seems high, but Salmon and Frank³³ found vaginal smears of the functional or estrogenic type consistently in 30 per cent of postmenopausal women, and intermittently with repeated smearing in another 30 per cent of postmenopausal women. In only 40 per cent were the smears consistently negative. Ayre and Bauld's findings are, therefore, of dubious significance, unless it can be demonstrated that such smears are significantly more frequent in the postmenopausal women with cancer than in postmenopausal women without cancer.

Other workers have stressed the findings of proliferative endometrium or endometrial hyperplasia with carcinoma of the uterus. This has also been used as evidence that excess endogenous estrogen causes the carcinoma. However, Fahlund and Broders¹⁸ compared the endometrium from postmenopausal women with adenocarcinoma of the corpus uteri to those without carcinoma. In their series they found "no appreciable difference in the percentage of cases of any given type of endometrium in adenocarcinomatous uteri as compared with non-adenocarcinomatous uteri, except with regard to atrophic endometrium." Atrophic endometrium (little or no estrogenic stimulation) was found more frequently in the carcinomatous than in the noncarcinomatous uterus.

The editorial in the *Journal of the American Medical Association* was limited to a summary of the original article by Ayre and Bauld. There was no critical evaluation of the literature on the subject.

whom seventy were treated with various preparations of vitamin B complex." According to these authors "the response to vitamin B complex therapy in these patients was usually prompt and often dramatic. Some of the patients showed only moderate improvement on oral therapy; as impairment of absorption and utilization occurs frequently in nutritional deficiency, these patients were given parenteral therapy in addition. With the latter, striking improvement, especially in premenstrual tension and in painful breasts, often occurred in as little as a few hours to at most a day or two."

Details were given on four patients, and more or less brief data were presented in tabular form on 43 more patients. With the exception of one 212-pound patient, body weight was not mentioned. No specific data were given as to the status of the endometrium, although it was stated that "studies on the endometriums of the cases with pathologic uterine bleeding are still under way."

In addition to the benefits in gynecologic disorders, the authors also credit the B complex therapy with other equally desirable effects. These include improvement of psoriasis, healing of intertrigo, clearing of acne, induction of the ability to tan rather than just sunburn, redistribution of fat so that while there was no weight loss, the circumference of excessively developed hips and breasts was reduced; disappearance of a mass from the breast that had been present for a decade, diminution in size (but not complete regression) of enlarged thyroids, and a clearing and brightening of the complexion.

Later in 1944 L. M. and M. S. Biskind¹³ reported an "accelerated postpartum involution of the uterus with vitamin B complex." One hundred seven control patients were judged to be consuming an adequate diet and were given no supplementary vitamins. Seventy-six treated patients were given B complex "solely for nutritional reasons when it became apparent that the average diet in pregnancy needed supplementation." Treatment was given only during pregnancy and not in the postpartum period. The degree or extent of postpartum involution at six weeks post partum was determined by bimanual examination.

This work was based "on the assumption that postpartum uterine subinvolution is related to excess estrogen, and that this excess is due to failure of destruction in the liver owing to deficiencies of the factors of the vitamin B complex." No evidence was presented that estrogen actually does or can cause subinvolution of the uterus. To our knowledge no such evidence exists.

In April, 1946, vitamin B complex deficiency (specifically thiamine and riboflavin) was implicated as a cause of cancer of the uterus as well as menorrhagia by Ayre and Bauld.³ Their observations included the findings in 150 patients with carcinoma of the uterus. According to these authors the "vaginal and cervical cytology smear" showed evidence of abnormally high endogenous estrogenic activity in two-thirds of the patients with uterine cancer.

Ayre and Bauld quoted extensively from the works of the Biskinds and, like them, believe that the cause of the excess endogenous estrogen (which caused the menorrhagia or the cancer) was an insufficiency of one or more of the vitamins of the B complex in the diet. This deficiency prevented the liver from carrying out its normal function of destroying or inactivating estrogen.

Detailed data were presented on three patients. All three "were bleeding excessively, and all showed abnormally high estrogen level in the cytology smears as well as thiamine deficiency" as judged by their response to a "vitamin-tolerance technique." The first of these patients, who was 29 years old, had either a "squamous intra-epithelial carcinoma" of the cervix or a "pre-cancerous secondary hyperplasia" of the cervix. The second was 14 years of age and her endometrium showed "overstimulated proliferative glands with mitosis and adenomatous formation such as would make the pathologist think

It is postulated in these clinical articles that excessive endogenous estrogens result from the inability of the vitamin deficient liver to inactivate them. In the Biskinds' articles no specific evidence has been presented that excessive estrogens actually are present. Ayre and Bauld state that evidence of the presence of excessive endogenous estrogens was in their vaginal and cervical cytology smears, yet they do not present evidence to substantiate this claim. The known physiology of the vagina makes it unlikely.

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Discussion

DR. JOHN W. HUFFMAN.—I would welcome the conviction that a deficiency of vitamin B-complex causes most of the common gynecologic complaints and that they could

Attention was drawn to the chemical "similarity" of estrogens and some of the true chemical carcinogens. This "similarity" has been commented on in many articles in the past. It consists of the presence of the phenanthrene nucleus as a part of the molecule in both estrogens and carcinogens. The implication, of course, is that the chemical similarity endows the estrogen with carcinogenic properties. The implication is not logical since androgens, progesterone, bile acids, cholesterol, and even vitamin D have this same phenanthrene nucleus as part of their molecular structure.

The editorial quotes an article by Henry²⁶—as did Ayre and Bauld—which reports "two cases in which the prolonged administration of diethylstilbestrol has been followed by the discovery of malignant growths in the uterus." Reading the original article reveals the fact that in neither of these patients could the many pathologists examining the tissues agree whether the tumors were malignant or not. Such findings are equivocal.

The rationale for treatment, the explanation for the unusually uniform and rather remarkable therapeutic response of the Biskinds' patients, as well as the theory behind the work of Ayre and Bauld, are necessarily based on the major assumption that vitamin B complex deficiency per se renders the liver incapable of inactivating estrogens.

Recently Drill and Pfeiffer¹⁴ have conclusively proved that the vitamin B complex deficiency was not the factor that made the liver unable to inactivate estrogen in the experimental animal, but that the real cause was the associated caloric deficiency. Every worker in this field has long been aware that the experimental animal on a B complex deficient diet refused to eat more than a very little, rapidly becomes emaciated, and eventually dies of self-induced starvation. Vital functions are, of course, at a minimum during starvation or even semistarvation. Drill wished to determine whether the inability of the liver to inactivate estrogens was due to the vitamin deficiency or due to the markedly reduced caloric intake. Accordingly, his control animals on a diet qualitatively normal were given each day exactly the same amount of food that the animals on the B complex deficient diet had eaten the day before. After approximately the same period of time the livers of *both* groups of animals lost their ability to inactivate the estrogen absorbed from the pellets implanted in their spleens. He demonstrated further that the phenomenon was due to inanition because of an inadequate caloric intake. Animals were given a calorically restricted diet and force fed with a more than adequate amount of the various vitamin B factors. In spite of all the added B vitamins, the livers of these animals also were unable to inactivate the estrogen.

Summary

This critical review of the literature is concerned with the function of the liver in the inactivation of estrogens; the effect of vitamin B complex deficiency on this function; the relation of vitamin B complex deficiency to various gynecologic disorders and to cancer of the uterus; and the therapeutic use of this substance in these conditions.

The clinical work is founded on the basic assumption that vitamin B complex deficiency renders the liver unable to inactivate estrogens. This leads to the accumulation of excessive endogenous estrogens which in turn cause the menorrhagia or may after prolonged action cause carcinoma of the uterus. The validity of the theory is evidently destroyed.

Anorexia and weight loss are early symptoms of vitamin B complex deficiency. The subjects of these articles were not reported as having had such symptoms. In fact, in one article it was specifically stated that most of the patients were overweight. It seems doubtful that these patients, at least, actually were deficient.

PREGNANCY ASSOCIATED WITH DIABETES*

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FROM Jan. 1, 1933, to Dec. 31, 1946, inclusive, 9,273 obstetric deliveries were made at the Mayo Clinic. The annual number of deliveries ranged from 384 in 1933 to 1,218 in 1946. In this period of fourteen years, we observed forty pregnant women who had diabetes. The forty diabetic women gave birth to fifty infants. No instance of multiple pregnancy was observed in these cases. Cesarean section was performed twenty-six times on twenty-two of the women. One of the infants delivered in this manner died in the neonatal period. Vaginal delivery was performed twenty-four times on nineteen of the women.† Of the twenty-four infants who were delivered through the vagina, fifteen survived, six were stillborn, and three died in the neonatal period. The fetal survival rate was 96.2 per cent in the instances in which cesarean section was performed, and 62.5 per cent in the instances in which the delivery was made through the vagina. All of the mothers survived. The clinical data in the two groups of cases are shown in Tables I and II.

In seven of the twenty-two cases in which cesarean section was performed, the patients previously had given birth to a dead fetus. In one of the seven cases, a stillbirth had occurred on two occasions. In four of the twenty-two cases, there was a history of neonatal death. One patient previously had been infertile, and dystocia previously had necessitated a difficult forceps delivery in one case. In three of the twenty-two cases in this group, the diabetes was difficult to control, and accident to the child was feared. Toxemia was present in eight cases. In one of the eight cases, toxemia occurred in two pregnancies in which the patient was observed at the clinic. Although the toxemia responded to treatment in some cases, it still was considered an added risk to the fetus. In five of the twenty-two cases in which cesarean section was performed, diabetes was the only complication. In several cases there was more than one indication for cesarean section.

We were able to select the method of delivery in thirty-one, or 62 per cent, of the fifty instances, that is, in all of the twenty-six instances in which cesarean section was performed and in five of the twenty-four instances in which vaginal delivery was employed. In two of the five instances in which vaginal delivery was selected, spontaneous labor occurred at or near term; in three instances, labor was induced. In six of the remaining nineteen instances in which vaginal delivery was employed, the fetus was dead. In thirteen instances, labor commenced prematurely and spontaneously while the fetus was alive.

The loss of nine of the twenty-four infants delivered through the vagina merits brief comment. In four instances the mother cooperated poorly in the care of the diabetes and severe acidosis no doubt contributed to the fetal mortality. The patient who had eclampsia came to the clinic for emergency treatment after the fetus had died in utero. In the case in which premature

*Read at the meeting of the Chicago Gynecological Society, Feb. 21 to 22, 1947.

†One of the forty patients was observed in four pregnancies. Cesarean section was performed once and vaginal delivery was employed on three occasions.

be relieved by its administration. To establish this conviction the proponents of the vitamin B complex deficiency theory ask us to accept certain reasoning, to wit: that the diets of a large group of women suffering from varied gynecologic disorders are seriously depleted of vitamin B complex; that the liver, due to this B-complex deficiency, fails to destroy estrogens; that a high estrogen level results because of this liver malfunction; that this estrogen level becomes high and remains high enough to produce menorrhagia, metrorrhagia, cystic mastitis, premenstrual tension, leucorrhea, uterine fibromyomas, fat pads about the hips, acne, muddy complexion, and carcinoma of the uterus; only this week dysmenorrhea was added to the list (all that remains to be added are threatened and habitual abortion). If we entertain this reasoning we may then, I think, properly ask the proponents of these hypotheses to show us by analysis of the diets of their patients that these diets were actually deficient in vitamin B complex. This they have not done. If we entertain this reasoning then we may expect its proponents to show us that these patients are actually deficient in vitamin B complex. This can be accomplished with a moderate degree of accuracy by a vitamin tolerance test. This was done in only a small group of patients. If we accept this reasoning we may expect its proponents to show us that the women they treated did have a high estrogen level as established by blood estrogen levels, even by estrogen excretion determinations. This they have not done. Last, we might properly expect these proponents to demonstrate to us that the many problems they attribute to a vitamin B complex deficiency actually are due to hyperestrogenism. I believe that many thoughtful clinical investigators are still unconvinced that hyperestrogenism is the principal cause for many of these ills. In addition, we might properly ask them to show us that women who suffer from these complaints and who do not exhibit clinical evidence of B-complex deficiency will be specifically benefited by its administration. There can be little doubt that individuals suffering from severe avitaminosis will have an impairment in their general health and that the genitals will participate in the derangements which are a part of that ill-health. Furthermore it is a common observation that vitamin-B complex does give a general sense of well-being and is of benefit in so-called "run-down" and under-par individuals. This is a far cry, however, from assigning to it, on the basis of present knowledge at least, a specific role in the causation and treatment of the many ills we have heard mentioned.

Again, I wish to say that I welcome the conviction that vitamin B complex will do the things that the proponents of this interesting hypothesis we have heard described claim for it. It will indeed be a relief to feel certain that I can forestall malignancy by its use and that I can treat the majority of the patients who come to me with one common panacea.

TABLE I. DATA IN TWENTY-TWO CASES IN WHICH CESAREAN SECTION WAS PERFORMED

| CASE | AGE (YR.) | GRAV- IDA | PARA | WEEKS OF GES- TATION | INFANT | | COMMENT |
|------|--------------|--------------|------|----------------------------|-----------------|-------|--|
| | | | | | WEIGHT (GM.) | FATE | |
| 1 | 29 | ii | i | 36 | 3,660 | Lived | Diabetes, grade 4, at 28 years; stillbirth at 26 years |
| 2 | 26 | iii | ii | 34 | 2,960 | Lived | Diabetes, grade 3, at 23 years; premature living infant as gravida i; stillbirth following diabetic coma as gravida ii |
| 3 | 33 | ii | i | 36 | 3,290 | Lived | Diabetes, grade 3, at 27 years; neonatal death of premature infant as gravida i; subsequent vaginal delivery of two premature infants, 2,520 Gm. (33 wk.) and 1,980 Gm. (31 wk.) respectively, both of whom survived |
| 4 | 22 | i | 0 | 36 | 3,310 | Lived | Diabetes, grade 4, at 20 years; severe ("brittle") diabetes; elective cesarean section |
| 5 | 41 | v | iii | 36 | 3,240 | Lived | Diabetes, grade 3, at first pregnancy at 34 years; patient uncooperative; first seen in severe acidosis in twenty-ninth week of pregnancy |
| 6 | 28 | ii | i | 37 | 2,970 | Lived | Diabetes, grade 3, at 25 years; first child stillborn |
| 7 | 30 | i | 0 | 33 | 1,900 | Lived | Diabetes, grade 3, at 26 years; patient first seen in severe toxemia which did not respond to treatment |
| 8 | 29 | iii | ii | 38 | 3,560 | Lived | Diabetes, grade 4, at 22 years; toxemia; ligation of tubes |
| 9 | 24 | ii | i | 36 | 3,670 | Lived | Diabetes, grade 3, in seventh month of first pregnancy at 22 years; stillbirth following acidosis |
| 10 | 26 | iii | ii | 35 | 3,830 | Lived | Sterilization |
| | 29 | ii | i | 36 | 2,870 | Lived | Diabetes, grade 3; mild toxemia; neonatal death of first child |
| 11 | 26 | i | 0 | 36 | 3,624 | Lived | Diabetes, grade 4, at 13 years; toxemia; severe retinitis |
| 12 | 27 | ii | i | 35 | 3,138 | Lived | Toxemia |
| | 24 | i | 0 | 36 | 3,240 | Lived | Diabetes, grade 3, at 17 years; toxemia which responded only partially to treatment |
| 13* | 27 | iii | ii | 33 | 3,120 | Lived | Diabetes, grade 4, at 16 years; neonatal death of first child; second child stillborn; subsequent vaginal delivery of premature infant that lived |
| 14 | 39 | ii | i | 36 | 2,760 | Lived | Diabetes, grade 4, at 24 years; premature stillbirth at 34 years; toxemia; ligation of tubes |
| 15 | 28 | ii | i | 38 | 3,360 | Lived | Diabetes, grade 4, at first pregnancy at 25 years; first child delivered alive with forceps; ligation of tubes |
| 16 | 23 | i | 0 | 36 | 2,780 | Lived | Diabetes discovered in pregnancy; elective cesarean section |
| 17 | 19 | i | 0 | 37 | 3,450 | Lived | Diabetes, grade 4, at 15 years; severe ("brittle") diabetes; coma once and severe acidosis once during pregnancy; toxemia which did not respond to treatment; subsequent premature delivery with neonatal death following diabetic coma 3 weeks previously and acidosis on admission to hospital |

separation of the placenta occurred, the diabetes was controlled satisfactorily and there was no evidence of toxemia. In one case, acidosis was present and no fetal heart sounds could be heard when the patient was admitted to the hospital. In two cases in which the diabetes was controlled satisfactorily and other complications were not present, the fetuses died in utero at the thirty-sixth and thirty-seventh weeks of pregnancy, respectively.

In 1936, Rynearson and I reported seven consecutive cases in which diabetic women were delivered of infants. Cesarean section was performed in six of the seven cases; in the remaining case, the infant was delivered through the vagina. Cesarean section was the treatment of choice at the time these patients were observed. We emphasized that hypoglycemia of the newborn infant was a frequent cause of neonatal morbidity and mortality, and we recommended that cesarean section at about the thirty-sixth week of gestation should be seriously considered for the delivery of the over-mature and overweight fetus of a diabetic woman. We advised watching for the development of hypoglycemia in the infant and stressed the importance of correcting this condition.

In the past ten years a considerable number of cases of diabetes and co-existing pregnancy have been reported. Until recently, the infant mortality and morbidity have not always been satisfactory, although the maternal risk has been minimal in cases in which adequate cooperation has existed between the patients and their physicians. A satisfactory explanation has not been found for the previously high incidence of infant mortality and morbidity. Perhaps the excellent work of Smith, Smith, and Hurwitz and of White will not serve to avoid all of the accidents to infants of diabetic mothers, for disturbances of metabolism incident to a combination of diabetes and pregnancy are necessarily complex. However, the results of correction of the imbalance between amounts of chorionic prolan and placental steroids resulted in a fetal salvage of 90 per cent, and White further reported a fetal survival rate of 96 per cent in cases in which diabetic mothers had a normal hormonal balance.

My experience with this concept of correction of hormonal imbalance is limited to eight cases. In six of these cases, the infants survived. Cesarean section was performed in two of these cases, and both of the infants lived. Toxemia was present in both of the cases and the diabetes was severe ("brittle") in one of the cases. In two cases, labor was induced at the thirty-fifth and thirty-eighth weeks of pregnancy, respectively, and live infants were delivered.

In four cases, labor commenced prematurely and delivery was made through the vagina. Premature separation of the placenta occurred in one of these cases. In this case, the child was stillborn. In one case, in which labor occurred at the thirtieth week of pregnancy, after coma and acidosis in the mother, the infant died in the neonatal period. In the two remaining cases, the infants lived. In one of these cases, the infant weighed 4,080 Gm. when born at the thirty-sixth week of gestation. In the other case, the infant weighed 4,210 Gm. and was delivered by a difficult forceps procedure.

It is to be hoped that recognition and correction of the hormonal imbalance, when present in diabetic women who are pregnant, will result in a higher

TABLE II. DATA IN NINETEEN CASES IN WHICH VAGINAL DELIVERY WAS EMPLOYED

| CASE | AGE YEARS | GRAVIDA | PARA | LABOR | PRE- MATURE RUPTURE OF MEM- BRANES | WEEKS OF GESTA- TION | INFANT | | COMMENT |
|------|--------------|---------|------|-------------|--|-------------------------------|-----------------|-------|---|
| | | | | | | | WEIGHT (GM.) | FATE | |
| 1 | 41 | xiii | ix | Spontaneous | + | 36 | 4,080 | Lived | Diabetes, grade 4, at 40 years; mother Rh negative |
| 2 | 35 | iii | ii | Spontaneous | + | 33 | 2,520 | Lived | Diabetes, grade 3, at 27 years; cesarean section as gravida ii, at 33 years, because of neonatal death of first child; acidosis when patient was admitted to hospital |
| 3 | 38 | iv | iii | Spontaneous | 0 | 31 | 1,980 | Lived | Hydrannios; retinitis |
| 4 | 31 | i | 0 | Spontaneous | + | 33 | 3,460 | Lived | Diabetes, grade 4, at 29 years; mild toxemia; outlet forceps |
| 5 | 36 | v | iii | Spontaneous | + | 36 | 3,640 | Lived | Diabetes, grade 4, at 34 years |
| 6 | 21 | i | 0 | Induced | 0 | 35 | 2,630 | Lived | Diabetes, grade 4, at 14 years; marked hydrannios; diabetic retinitis; albuminuria, grade 3; edema, grade 2 |
| 7 | 32 | viii | vi | Spontaneous | 0 | 36 | 3,620 | Lived | Diabetes discovered in this pregnancy |
| 8 | 31 | iii | ii | Induced | + | 38 | 3,360 | Lived | Diabetes, grade 4, at 18 years; stillbirth at 21 years; second pregnancy (living child) at 24 years; retinitis |
| 9 | 29 | i | 0 | Induced | + | 38 | 4,210 | Lived | Diabetes at 12 years; toxemia; low forceps |
| 10 | 31 | iii | ii | | | 40 | 3,216 | Lived | Diabetes at 26 years |
| 10 | 17 | i | 0 | Spontaneous | + | 36 | 3,460 | Lived | Diabetes, grade 4, at 13 years; hypertension |

TABLE I.—CONT'D

| CASE | AGE (YR.) | GRAV- IDA | PARA | WEEKS OF GES- TATION | INFANT | | COMMENT |
|------|--------------|--------------|------|----------------------------|-----------------|-----------------|---|
| | | | | | WEIGHT (GM.) | FATE | |
| 18 | 27 | i | 0 | 37 | 2,460 | Lived | Diabetes, grade 4, at 16 years; severe ("brittle") diabetes; toxemia |
| 19 | 36 | v | iv | 37 | 3,402 | Lived | Diabetes, grade 3, at 30 years; first pregnancy terminated at sixth month; second pregnancy terminated at eighth month; third pregnancy terminated at seventh month (live child); fourth pregnancy terminated at seventh month (neonatal death) |
| 20 | 29 | i | 0 | 37 | 3,175 | Lived | Diabetes at 24 years; elective cesarean section |
| 21 | 23 | iii | i | 36 | 3,040 | Lived | Diabetes at 19 years; two previous stillbirths; elective cesarean section |
| 22 | 32 | i | 0 | 37 | 3,941 | Lived | Diabetes, grade 4, at 28 years; previous infertility |
| | 36 | ii | i | 36 | 3,624 | Lived | Elective cesarean section |
| | 38 | iii | ii | 35 | 3,804 | Neo-natal death | Elective cesarean section; ligation of tubes |

*This is the same case as Case 12 in Table II. Although the cases in this table and Table II total forty-one, there were only forty diabetic patients.

percentage of normal deliveries. As is true in all obstetric conditions, a careful study of all factors involved in a given case should lead to proper selection of treatment. There is and will continue to be a difference of opinion in regard to the delivery of diabetic women.

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3. White, Priscilla: J. A. M. A. 128: 181-182, 1945.

Discussion

DR. M. DAVID ALLWEISS.—We can certainly say that there is agreement in the literature that the pregnant diabetic must be controlled and well regulated. This is not a big problem in the cooperative patient where the use of protamine insulin with a fuller diet and small doses of regular insulin have made this problem minor.

The second problem is that of the newborn infant. This has interested us and we have found that hypoglycemia occurs within the first fifty minutes after birth. This is corrected with glucose given to the infant by mouth.

The third problem is the one presented by White in hormone imbalance. We have followed the literature carefully on this but we have had no experience with it. We have not had the toxemia others have reported.

The fourth problem is that of delivery. As an internist, we can give this problem back to the obstetrician. Dr. Randall infers that he believes in cesarean section. We believe in it, too, because out of 39 patients 36 have been sectioned with no infant mortality. Of the three delivering from below, two infants died.

One of the most important things I got out of Dr. Randall's paper is this: If the infant is small and if labor could be induced at about thirty-six weeks and the patient be delivered from below, a live baby would be the result. Several of his patients went into spontaneous labor around the thirty-sixth week and still the baby died. We do not know the answer for this. Perhaps it is the large, bulky baby being pulled through the vaginal

canal and not strong enough to withstand the trauma as do normal babies delivered spontaneously. When the diabetic pregnant person presents herself to an obstetrician she wants a live baby, and apparently the way to get it is by cesarean section at about the thirty-sixth week, good care of the mother throughout pregnancy, and special care to the infant within the first fifty minutes after birth.

DR. CHESTER COGGESHALL.—I suspect that Dr. Randall presented this conservative paper on his experiences with pregnancy and diabetes for one very valid reason: that the cold facts presented here could bear more weight than anything else.

Both the treatment of diabetes and of pregnancy associated with diabetes are relatively new medical approaches dating from the discovery of insulin. Prior to insulin few women of the childbearing age with diabetes became pregnant. Many were nonovulatory and many had primary amenorrhea.

I am sure that Dr. Randall has not presented this paper with the purpose of offering cesarean section as the answer to the high fetal mortality rate in this condition, and obviously his second group of diabetics delivered vaginally bears this out. Cesarean section is not the answer to the high percentage of stillbirths.

I was fortunate in being associated with Dr. White when she began her very interesting work. The amount of adverse criticism was tremendous at that time both within our own group in Boston and throughout the country. Since that time I have found that the internist feels that Dr. White has contributed greatly in her study of abnormal hormonal balance in the diabetic pregnant woman. I called her last night because I know how keenly she feels about this subject and I am privileged to give you a brief, up-to-date report of her latest cases: of 336 diabetic pregnant women since January, 1936, 71 had normal hormonal balance as determined by her study; there were two deaths in that series, or a fetal survival rate of 97 per cent. Sixty-one patients showed abnormal hormonal balance as determined by her study, and were not treated but were used as controls; in that group she obtained 44 per cent fetal survival rate. Two hundred four abnormal hormonal balance cases were treated by the use of large doses of stilbesterol, and in this series Dr. White obtained a 90.5 per cent fetal survival rate.

Dr. Randall's paper and the statistics from any large pregnancy series concerned with diabetes will bear out that these are remarkable figures of Dr. White. They should be of great interest and should force upon the obstetrician a program of definite observation and treatment along medical lines and a program of research.

What should be your role in the pregnant diabetic? First of all I think it is important to establish whether it is a true diabetes or not. I think the management of the diabetes should be given over to an internist especially qualified in the subject. I think, as Dr. White does, that we should not rely upon the older signs of impending toxemia, such as edema, albuminuria, rising blood pressure, but that by thorough investigative work the excretion studies of pregnandiol should be made. Dr. White believes that a simple method of examining vaginal smears for the disappearance of basophilic cells may be of some help to the obstetrician who practices without a laboratory.

The most important consideration, as you see these diabetic women, is to realize what diabetes really means to that patient. I am grieved to have to state that, despite the admirable weapons we have for its treatment, the longer the patient with diabetes is kept alive, the more surely we see signs of degeneration, particularly arteriosclerosis. They are prematurely aged individuals. It may be the arteriosclerosis itself or it may be, as Dr. White suggested, secondary premature ovarian failure which accounts for the high amount of toxemia in these pregnant women. I think Dr. Randall's paper bears out the fact that the longer the diabetes has been present, the greater the chance of toxemia and the more necessary the choice of early delivery by cesarean section until we have learned more about the subject.

DR. EDWARD L. CORNELL.—I agree thoroughly with Dr. Coggeshall that these patients should be under the care of a man competent to control the diabetes. That is a primary factor in order to secure a live baby.

| | | | | | | | | | |
|-----|----|------|-----|-------------|---|----|-------|-------------------------|--|
| 11 | 31 | v | iv | Spontaneous | 0 | 37 | 2,964 | Stillborn and macerated | Diabetes, grade 2 |
| | 37 | viii | vii | Spontaneous | | 36 | 3,020 | Mongolian idiot, lived | |
| 12* | 23 | i | 0 | Spontaneous | + | 26 | 1,540 | Neonatal death | Diabetes, grade 4, at 16 years; hydramnios, grade 2; patient uncooperative |
| | 24 | ii | i | Spontaneous | + | 34 | 2,860 | Stillborn | Hydramnios, grade 2; patient admitted in acidosis |
| 13 | 29 | iv | iii | Spontaneous | + | 33 | 2,230 | Lived | Hydramnios, grade 2 |
| | 20 | ii | 0 | Spontaneous | 0 | 35 | 1,980 | Neonatal death | Diabetes, grade 4, at 19 years; patient uncooperative |
| 14 | 24 | iv | iii | Spontaneous | 0 | 32 | 2,450 | Lived | Infant had congenital cardiac defect |
| | 37 | ii | i | Induced | + | 36 | 3,460 | Stillborn | Diabetes at 33 years; labor induced because of death of fetus |
| 15 | 27 | i | 0 | Induced | 0 | 37 | | Stillborn | Diabetes, grade 3, at 23 years; patient admitted with eclampsia and dead fetus in uterus |
| 16 | 22 | i | 0 | Spontaneous | 0 | 30 | | Neonatal death | Diabetes, grade 4, at 15 years; patient uncooperative |
| 17 | 25 | ii | 0 | Spontaneous | 0 | 33 | 2,440 | Stillborn | Diabetes at 14 years; toxemia; patient uncooperative |
| 18 | 26 | iii | ii | | | 37 | 3,580 | Stillborn | Premature separation of placenta |
| 19 | 28 | ii | i | Spontaneous | 0 | 38 | 3,630 | Lived | |

*This is the same case as Case 13 in Table I. Although the cases in this table and Table I total forty-one, there were only forty diabetic patients.

THE TREATMENT OF CARCINOMA OF THE VULVA*

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THERE is still considerable confusion as to the effectiveness of the various forms of therapy which are being advocated and used for vulvar carcinoma. This is apparently due to the fact that the disease is comparatively rare, and few investigators have had sufficient experience with it to justify dogmatic conclusions. Many have not hesitated to express unproved opinions, but one can only be surprised on reading the literature to realize how little factual support there is for such opinions. The outstanding exception is the work of Taussig. In spite of this, two rather disturbing facts must be faced. Papers are appearing which advocate extensive surgical procedures without any statement as to their applicability or results. Second, one cannot escape the fact that a large proportion of patients with this disease are in actual practice being handled by demonstrably ineffective measures which effectively preclude a reasonable chance of subsequent cure.

Those who have to deal with the problem must decide on some form of attack. It is the object of this paper to attempt to evaluate the results of such a decision at the University of Minnesota Medical School, to compare the results of the presently used radical vulvectomy with other types of procedures previously used, and to present what information has come from the material in regard to the further extension of the surgical attack.

The material represents all of the vulvar carcinomas seen from 1928 to the end of 1946 and is shown in Table I. It falls into two groups. Prior to September, 1938, the thirty-six patients were treated by a wide variety of measures including simple vulvectomy, unilateral and bilateral superficial, and both superficial and deep gland removal, x-ray to groin, and/or to vulva, and radium or radon application to vulva or groin. These were done at various time intervals and in various combinations so that there were nearly half as many types of procedures used as there were patients. This sort of extensive individualization of therapy had certain advantages, but can now be tested for curative results. No single stage radical vulvectomy was used. This material has been described in more detail elsewhere.⁷

In September, 1938, an attempt to standardize therapy was introduced. The radical vulvectomy to be described was used and its applicability to the group is shown in the table.

The radical vulvectomy which was used has not varied significantly except as necessary to handle the variations of extension of the tumor to urethra, vagina, or perirectal glands. Occasionally in the more extensive tumors, radon

*Presented before the Chicago Gynecological Society, February 21, 1947.

I have not used cesarean section routinely for the delivery of these patients. I have endeavored to select the cases. If they give a history of previous stillbirths or miscarriages, cesarean section is certainly advised as soon as the baby is viable. I usually have an x-ray taken to try to determine the size of the baby.

I want to caution that these babies should be watched carefully after delivery because they seem to be poor risks. Hypoglycemia and other problems arise so the obstetrician should be on the alert at all times in the management of these babies during the first ten days of life.

Toxemia in my experience has not been as frequent as it has in Dr. Randall's series. I see it occasionally.

I would like to ask Dr. Randall what method of induction of labor he employs in those patients delivered vaginally.

DR. RANDALL (Closing).—As I have said before, I am not too happy about our experiences in this condition. I think it can be improved. I think the points brought out by the discussants serve to emphasize that these patients are problems that we have to take care of in conjunction with the internist. I should pay particular tribute to the pediatric staff who watched these babies carefully after they were born.

As to the method of induction of labor, mostly we have ruptured the membranes. We have, however, been extremely loath to induce labor in this manner in a primigravid woman of thirty-five to thirty-six weeks. Too frequently under these circumstances the cervix is uneffaced and the resulting labor is likely to be increased in length, and I doubt that the infant of a diabetic mother should be subjected to a prolonged labor. It seems to me that cesarean section is better treatment.

TABLE I. CARCINOMA OF THE VULVA, 1928 TO 1946

| | | |
|---|----|---|
| Total | 80 | |
| To Sept., 1938 | 36 | |
| Not treated | 4 | 4 Died of carcinoma |
| Treated | 32 | 26 Died 2 postoperative emboli |
| (no radical vulvectomy) | | Died 1 vascular disease—19 months; no tumor |
| | | Died 23 carcinoma |
| | 5 | Alive and cured 5 years or more |
| | 1 | Alive with tumor—150 months |
| Sept., 1938-1946 | 44 | |
| Not treated | 4 | 3 Died of carcinoma |
| | | 1 Alive with tumor 62 months |
| Treated (radical vulvectomy) | 38 | 15 Died 1 postoperative embolus |
| | | Died 1 postoperative pyelonephritis |
| | | Died 1 heart block pre- and postoperative |
| | | Died 1 ? cause, postoperative |
| | | Died 3 apoplexy at 2, 4, and 59 months; no tumor |
| | | Died 1 accidental at 40 months; no tumor |
| | | Died 7 carcinoma |
| | 4 | Alive and cured 5 years or more |
| | 18 | Alive, no tumor, 2 to 59 months |
| | 1 | Alive with tumor, 46 months |
| Treated (other than radical vulvectomy) | 1 | 1 Alive and cured 70 months (microscopic tumor simple vulvectomy) |
| | 1 | 1 Alive with tumor, 41 months (probably carcinoma of vagina) |

a mortality rate of 6 per cent. Both of these followed simple vulvectomy. Of the remaining 24 who died, 23 died of carcinoma of the vulva. This is surprising, since one would expect considerably greater interference with the cure rate from deaths due to noncarcinomatous causes in a disease of such relatively advanced age as this. Five are alive and free of tumor five years or more after treatment for an absolute cure rate of 13.9 per cent or a relative cure rate of 15.6 per cent. These five patients have been alive and free of tumor from 101 to 222 months. Four had simple vulvectomies and x-ray to the groin. One of these had a unilateral gland dissection at a later time with no tumor found in the glands. The fifth patient had a local excision, x-ray to the groin, and radon to the vulvar lesion. Local recurrences were treated on several occasions. She has survived for 15 years without further recurrence. All of these were early lesions.

This then would seem to represent the curative possibilities of an individualized therapy based upon simple vulvectomy followed at various intervals by local inguinal and femoral gland dissection and irradiation of various sorts.

There are good theoretical reasons for excluding irradiation as an effective attack. In this group, it seems to have been without curative effect except under the most unusual circumstances of localization and small early tumor.

In the second group treated since September, 1938, there were 44 patients. Two of these may reasonably be excluded from consideration. One presented complaints of persistent pruritis and the finding of kraurosis. Biopsy showed no tumor. A simple vulvectomy was done, and the routine sections of the surgical material showed no tumor. Further search was done by the department and an extremely early carcinoma found. It was decided to do nothing further, and the patient is alive and free of tumor 70 months after operation. The second patient was 80 years of age and could scarcely walk. She had trophic ulcers on both lower legs. She had an undifferentiated squamous cell carcinoma which involved the lower part of the anterior vaginal wall and the lower portion of the vestibule and urethra. From histologic appearance this

seeds have been applied at operation to the margin of the incision closest to the tumor to deliver 7 erythema skin doses (7,000 gamma roentgens) to an area 1 cm. wide. Local 0.5 per cent procaine, with or without adrenalin 1-1,000, up to 3 drops per 30 c.c. of solution depending upon the usual criteria for this, was used on all. Preparation for this involves the exhibition of 6 grains of sodium amytal three hours before operation. The patient is seen one and one-half hours later when a further 3 grains of sodium amytal may or may not be added depending on age, size, and response. Hyoscine in doses of $\frac{1}{150}$ or $\frac{1}{200}$ is given at this time. Demerol or morphia may occasionally be added during the operation. The finer details of the infiltration technique need not concern us here. Strict precautions are taken to avoid infiltrating tumor-bearing tissue. It is necessary to reinfiltrate the femoral and inguinal canal regions and that of the clitoris as these are approached. A wide mass of lymphatic-bearing fat is dissected out from what is usually an approximation of the superficial lamella down to the fascia lata, the external oblique muscle, and the periosteum of the symphysis, and this is left attached medially. The inguinal canal is usually opened, but under any circumstances is cleaned of its lymphatic-bearing fat to the peritoneum. The upper 5-6 cm. of the saphenous vein is removed. The cribriform fascia is removed, and the femoral canal cleaned of its lymphatic tissue to the peritoneum. Hernial closures are done on both femoral and inguinal canals. An operator and assistant on each side allows this dissection to be done on the two sides simultaneously. Various amounts of skin are removed and closure done. The vulva is then infiltrated with procaine solution, and a wide excision is carried out removing all of the subcutaneous fat and as much of the vulvar skin and vagina as possible. Leucoplakic skin about the anus is also removed, but the anus is not circumcised when tumor does not involve this area. One can better avoid anal strictures by removing the remainder of the leucoplakia at a second sitting after healing of the partial excision. The whole mass is thus removed in one piece. The vulva area is closed as completely as possible. A retention catheter is placed and the wound dressed with sea sponges and elastic tape for pressure. The patients are allowed out of bed and walk on the day of operation and each day thereafter. Many of the wounds break down and secondary closures or pinch grafting is done later as indicated.

A word might be said here as to the use of local anesthesia. It requires a good deal from the operator. He must obtain the confidence of his patient. There is little skill required for its application but it prolongs the operation and requires gentleness and patience. What discomfort there is for the patient seems to be more than offset by its safety. It alone has allowed wide applicability of curative surgical attempts to many of these patients. Their ages ranged from 36 to 84 years, with three over 80 years and eleven between 70 and 80 years. No patient was excluded from operation because of general physical disability. Of the six who were not treated by radical vulvectomy, three had hopeless tumors for even palliation, one refused treatment, one was treated as a carcinoma of the vagina, and one had a microscopic tumor. The earliest postoperative death was on the sixteenth postoperative day. No death had any direct relationship to the surgical procedure itself or to the anesthesia. About two-thirds of the patients have no or very little memory of the operative day. In our hands it has given satisfactory pain relief.

There were 36 patients seen prior to September, 1938 (Table I). Four were not treated, all because of hopelessly extensive tumors. That these were well excluded is shown by the fact that three died in less than a month and one in ten months, all of carcinoma. The general nature of the treatment of the remaining 32 patients was indicated above, but none were treated by radical vulvectomy. There were only two deaths in the postoperative period for

eter involving the labium majus and minus on one side. She died of a pulmonary embolus on the twenty-second postoperative day. One was 84 years old, developed uremia due to pyelonephritis, and died on the forty-first postoperative day. She had a 6 cm. tumor of one labium majus. One was 74 years old with a 6 cm. tumor of labium majus and minus and metastatic tumor in the inguinal and femoral glands. She had diabetes and a bundle branch block before operation. She died of cardiac failure on the sixteenth postoperative day. The fourth was 73 years old and had a 2 cm. tumor of the labium majus and diabetes. She simply faded away to die on the forty-third postoperative day with no adequate diagnosis. Autopsy was refused. It seems clear that in all of these, the operative procedure was responsible for at least shortening the life of the patient. All have survived the operative procedure itself to die of complications later. However, whatever one may conclude as to the propriety of the indications for operating upon these patients, it would seem wise to consider the 10 per cent operative mortality as real.

Four patients have died at two, four, forty, and fifty-nine months after operation of other than malignant disease. None of these had evidence of recurrent tumor at the time of death. One other patient is alive and has recurrent tumor forty-six months after operation.

Only seven of those who were exposed to radical vulvectomy have died of carcinoma. The survival rates for these are shown in Fig. 1. There will undoubtedly be more as time passes, but it is not possible that this will reach the proportion dying of carcinoma after treatment by lesser means than radical vulvectomy. One is tempted to conclude that radical vulvectomy is a fairly effective means of removing the carcinoma.

This conclusion is further supported by the group of four who are alive and free of tumor more than five years. There are 15 patients who were seen more than five years ago and since the radical vulvectomy was introduced. Two of these were among those described above as untreatable. There were two operative deaths and the microscopic tumor treated by simple vulvectomy and described above. Of the remaining ten patients, four are alive and free of tumor, and two died without tumor but of other causes. There were then 4 carcinoma deaths of 10 patients who survived the radical vulvectomy by comparison with 23 carcinoma deaths of the 30 who survived the lesser procedures.

There are 18 patients who have had radical vulvectomies and who have survived without tumor from two to fifty-nine months. The duration of survival of these is shown in the insert in the upper right of Fig. 1. One can use various means to calculate the expected proportion of five-year cures from this group. This is inaccurate but, from whatever approach, it is apparent that the radical vulvectomy will produce several times the cure rate of the lesser procedures.

There are two melanosarcomas in this series, both of whom have had radical vulvectomy and who have survived without recurrence for thirty-six and forty-two months:

Some conclusions appear to be justified. The various types of therapy which do not include a single stage removal of inguinal and femoral glands intact with the radical removal of vulva and adjacent structures when necessary, will produce only about 15 per cent of five-year cures. A considerable proportion of patients so treated will survive for quite long periods of time as will those who are not treated at all. Because of the nature of the disease and the nasty symptomatology, this survival is a questionable advantage.

There is no evidence from this material that irradiation in any form has played any significant role in curing the lesion. It appears to be even less useful as a palliative measure. There are valid theoretical reasons for this.

was more likely a carcinoma of the vagina. It is doubtful where it belongs, but it was treated by local excision and radon seeds. It has recurred and been retreated, but the patient is alive with recurrence which has been retreated after forty-one months.

This would leave 42 patients of whom 38 were treated by radical vulvectomy for an applicability rate of 90.5 per cent. Four patients were not treated. One was 63 years old and had been treated elsewhere by local vulvectomy followed by x-ray to the groins. There was a large mass of involved inguinal and femoral glands and a large tumor mass which extended the whole right side of the abdomen. She died in three months of carcinoma. The second

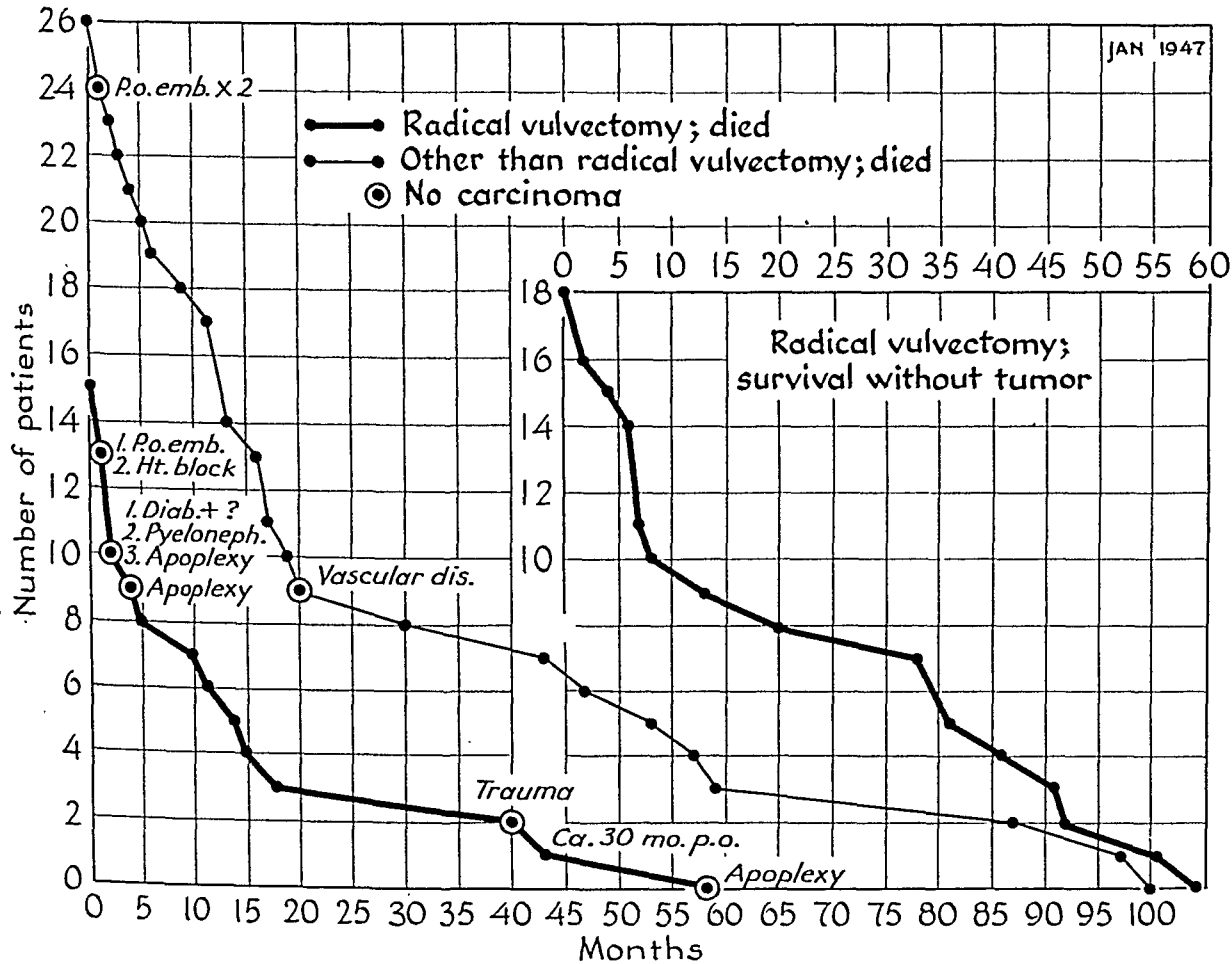


Fig. 1.—Survival of treated carcinoma of the vulva.

was 82 years of age, had a 10 cm. tumor, was obese, and showed advanced senility. She died in six months of carcinoma. The third was 84 years old and had been treated elsewhere by local excision, x-ray, and radium. She had a large tumor involving both labia, vestibule, clitoris, urethra, and the lower 4 cm. of the vagina. She also had pernicious anemia and was so senile that her answers to questions were quite irrelevant. She died seven months later of carcinoma. The fourth was a 40-year-old prostitute with a treatable tumor. For reasons of her own, she refused surgical therapy. She is alive with the tumor sixty-two months later!

Of the 38 patients who were treated by radical vulvectomy, 15 have died. Of these, four must be charged as postoperative deaths for a mortality rate of 10.5 per cent. One of these was 63 years old and had a tumor 2 cm. in diam-

There are a number of unsolved problems. A large proportion of the wounds break down as a result of skin necrosis. This has been ascribed to various causes. A number of procedures have been tried in an attempt to avoid this. Leaving the wound open and applying dermatome grafts at the original operation made no improvement. Pressure dressings have only partially improved the results. The use of penicillin and the sulfonamides has not changed it. Experience has made it clear that the less undermined skin which is left the better the primary healing will be. It is wrong to sacrifice the wide removal of lymphatic-bearing fat or to attempt to excise the vulva or vagina too close to the tumor for the purpose of obtaining healing. Subsequent skin grafting or secondary closure is a satisfactory substitute, although this involves prolonged hospitalization in preparation for it.

In view of the fact that there are three deaths from embolism among the 80 patients, consideration will have to be given to vein ligation at the time of radical vulvectomy. This has not yet been done.

Extension of the operation to include removal of lymphatic structures along the femoral and iliac vessels within the pelvis, as has been advocated, has not been done for various reasons. One finds it hard to believe that this would be applicable to more than a few of the younger patients. It is a formidable operation, and if this involves the sacrifice of the single stage bilateral femoral and inguinal gland removal without cutting through the lymphatic bearing area, it does not satisfy the requirements which seem to be indicated in this study. There is no acceptable proof available at present as to the operative mortality involved but it is reasonable to assume that it will be considerably higher than that of radical vulvectomy as here described, if it be applied to other than an occasional selected patient. The numbers which can be cured when pelvic gland involvement is demonstrated are not yet known. The most serious argument against it lies in the fact that of the seven patients in this series who died of carcinoma following radical vulvectomy, every single one had local tumor on the surface of the vulva, symphysis, groin or vagina. Perhaps when we have learned to control this, it will be time enough to consider intrapelvic gland dissection.

It would appear from this material that the criterion of the five-year cure rate is a useful and reasonable expression of the results of treatment of carcinoma of the vulva.

Summary

1. Carcinoma of the vulva treated by a wide variety of combinations of simple vulvectomy, radium and x-ray, and with or without later unilateral or bilateral superficial or superficial and deep inguinal gland dissection produced an absolute cure rate of 13.9 per cent and a relative cure rate of 15.6 per cent.

2. In a second series, radical vulvectomy as described was applicable to 90.5 per cent. Of 38 patients so treated, 4 are alive and well more than five years after operation and 18 are alive and free of tumor for from two to fifty-nine months. This represents a significant improvement.

Radical vulvectomy has improved the results significantly. Just what can be done with it is still open to question, since it has been applied here to 90 per cent of the tumors seen. Many of these were tumors which had been treated elsewhere by means which not only wasted considerable time, but interfered with the effective application of radical vulvectomy. Many were tumors which were only referred for treatment late in the course of the disease and who were treated mainly for palliative purposes. Sufficient time has not yet elapsed to justify relating the size of the tumor and its position to results which can be obtained by radical vulvectomy. That this is the most important feature affecting results is perfectly clear and, for what it may be worth, it can be said that in our experience, early carcinoma of the vulva other than that of the clitoris, is curable in a very large proportion of instances if radical procedures are undertaken at once. There has been sufficient experience with early tumors treated by other than radical vulvectomy to make it clear that minor procedures are not satisfactory. Local excision or local irradiation has no place in the treatment of early tumors. It seems clear that carcinoma of the vulva, particularly that of the labia majora, is a generalized disease and that the multiple nodules or recurrences are more often new areas of tumor than metastases or residual tumor from the main mass. To remove the vulva alone is to fail to take advantage of perhaps the most important clinical feature of the disease, which is the fact that lymphatic metastases tend to remain for reasonably long periods of time in the inguinal and femoral areas without spread beyond this. The presence or absence of palpable glands is no useful criterion as to presence or absence of tumor in this area. Contralateral gland involvement is so well known that the bilateral gland removal needs no support here. In view of all of this, it seems justified to conclude that the early cases should be treated by radical vulvectomy, and experience with this has shown it to be remarkably effective.

One would like to energetically oppose the carrying out of gland removal for biopsy. It serves no useful purpose since the glands are to be removed intact later. It involves opening into possible tumor-bearing tissue. It can make clean removal of the gland-bearing mass impossible.

It is hard to prove or disprove the wisdom of using radical vulvectomy in the advanced tumors. Survival rates for lesser procedures are shown in Table I. One suspects that those who experienced the longer survivals might have been cured by more radical approach although this cannot, of course, be proved. Otherwise, the survival rates for the lesser procedures and for radical vulvectomy are similar. To rid the patient even temporarily of ulcerated stinking masses is to make a significant contribution to their welfare. Surprising results are not unusual, and there are several patients among those who are surviving without tumor for long periods of time who were refused any interference by competent gynecologists. The applicability rate of radical vulvectomy here reported is an expression of the policy of applying it wherever even a reasonable hope of palliation exists. It appears to be justified. Statistical proof of the propriety of this must be postponed.

cause of the considerable amount of serous drainage, and plasma may be administered in some cases. The patients are allowed to be on their feet forty-eight hours after operation and are discharged within a few days when the wound looks comparatively clean. The patients are given an ointment of 5 per cent boric acid and scarlet red to apply locally and they are advised to abduct their limbs.

In conclusion, I wish to state decisively that radiation therapy has little value in the treatment of carcinoma of the vulva and that radical surgery has been my treatment of choice as carried out by Dr. McKelvey.

I wish to take this opportunity to thank the Chicago Gynecological Society for the privilege of discussing this paper, and once again wish to commend Dr. McKelvey on his timely presentation.

DR. H. O. JONES.—Dr. McKelvey suggests that ineffective measures of treatment and inaccurate reports make systematic study of results impossible. This is especially true of the more or less rare diseases. No one clinic has a sufficient number of such cases to offer an accurate statistical report. Should such methods as suggested in this paper be followed, combinations of different reports would be most valuable.

We have followed the procedure advocated by the essayist and are quite certain the incomplete operation is inadequate. Recently we have had a patient die from hemorrhage due to erosion of the femoral artery by a metastatic carcinomatous nodule in a lymph gland treated at another hospital by the incomplete operation. We agree, furthermore, that x-ray is of little demonstrable value. We differ in our outlook upon the prognosis depending upon the location of the malignancy. We believe it is directly proportionate to the presence of lymph node involvement. It is true the areas mentioned by McKelvey are more prone to extension than those more favorably situated. Furthermore, as Taussig has pointed out, the cell type is of utmost importance. We believe, as he did, that the carcinoma in situ rarely, if ever, can be identified. It is, as Bowen's disease, relatively benign. So we must agree again with the author and Taussig that the real improvement in cures depends upon how early the diagnosis is made and how thorough the treatment.

More than 60 per cent of our cases have been associated with leucoplakia of the vulva and, having seen these lesions develop while x-ray and palliative procedures were being applied to the leucoplakia, we have treated this lesion radically.

I would urge all to join with McKelvey and standardize our reports to conform to a pattern to further the studies of this malignant disease.

DR. EDWARD ALLEN.—I would like to hear Dr. McKelvey say something about the preoperative treatment of these patients.

DR. McKELVEY (Closing).—There is little to add about the use of local anesthesia that has not already been said. We have been more worried about the possibility of disturbing the tumor itself than we have with the question of healing. I am satisfied that healing has no relation to the anesthesia. That is said for many reasons. In cesarean section, local anesthesia produces wounds that heal satisfactorily. Experience with the use of local anesthesia in simple vulvectomy in which there is a comparable degree of local removal of tissue produces complete healing. The surgeon treating melanosarcoma of the lower extremity does a similar inguinal dissection that follows the lymphatics down somewhat farther into the leg than we feel justified in doing. These are done under general anesthesia and produce exactly the same lack of primary healing. Careful observation of these wounds leads to the following conclusions. The amount of undermined tissue that has to be left behind will determine the proportion of skin breakdown. Where breakdown occurs there is first reddening of the skin associated with edema. Very gradually that skin becomes dusky and necrotic and sloughs away on the seventh to tenth day. Blueing appears on the fifth day. We are dealing here with a vascular problem of some sort. We thought at first it was a disturbed lymphatic supply which interfered with the blood supply, but I am not sure that is the explanation. I am sure it is not related to the local anesthesia.

3. Some of the problems of the treatment of carcinoma of the vulva are discussed. Reasons are presented for the choice of this type of radical vulvectomy as opposed to lesser procedures and to further extension of the operation.

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Discussion

DR. R. E. CAMPBELL, Madison, Wis.—Dr. McKelvey is to be commended for this thorough study of carcinoma of the vulva, especially at a time when its treatment is in such a state of flux. I quite agree with him that at the present time there are as many different types of treatment as patients. It is only by studies such as this, in which the critical analysis has been both destructive and constructive, that treatment in medicine can go forward.

I have had a considerable experience with carcinoma of the vulva, having seen in the last twenty years probably over 100 cases. Earlier in my experience I was in the same dilemma as everyone else concerning the treatment of this condition. However, with the advent of Dr. Taussig's monumental reports of his experiences by radical surgery, I developed a new enthusiasm for treating this condition, and certainly the patient was given a new lease on life. Because of limitation of time I was unable to get a report of my cases to give at this time, but it is my intention to reflect my experiences in this discussion.

Dr. McKelvey has shown that in patients treated prior to 1938 the results were anything but favorable; in 32 of the 36 cases none was treated by radical vulvectomy and in this series there were 25 deaths and only 5 patients were alive and cured at the end of five years. The answer to these results is so obvious in comparison with the results of cases treated from 1938 to 1946 by radical surgery that it needs no further comment.

It is of greatest importance to note that in the series of 38 cases treated by radical surgery, there were only 15 deaths, 4 of which were charged as postoperative deaths, giving a mortality rate of 10.5 per cent. A great deal of emphasis should be placed upon the fact that four patients of this series are alive and cured after a five-year period, 18 are alive with no tumors from 2 to 59 months following treatment but it must be realized that undoubtedly some of these may succumb to the disease later on. One patient has had a prolongation of life of 46 months with a tumor still present. In further analysis of these figures it can be said that in the series of 38 cases treated by radical surgery, 22 are alive with no tumor, giving a percentage cure of 59 per cent at the present time, and this result is commendable.

Local anesthesia is important in these cases but infiltration of the tumor must be avoided. Dr. McKelvey uses two operative teams in his gland resections which is an excellent procedure for saving time.

So far as radiation therapy is concerned, I agree that it may be coupled with radical surgery in the more extensive lesions. In the radical operation where the glands are highly malignant, postoperative radiation therapy possibly might be indicated. It may also be the choice where patients refuse surgery, as it does have some palliative value.

It may be of interest that in my cases I have commonly left the vulvectomy wounds wide open without attempting to close them and it is remarkable how they will granulate in and epithelialize over. The blood proteins in these patients are carefully watched be-

THE CHARACTERISTICS OF UTERINE BLEEDING FOLLOWING CYCLIC ORAL THERAPY WITH ESTROGEN AND PROGESTERONE*

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THE effects of estrogen and progesterone therapy on the latent period and on the duration of uterine bleeding in monkeys have been studied in considerable detail.¹ Since the cycles of monkeys in many respects resemble those of women,² these data on the monkey have been translated to woman without complete experimental confirmation. The general impression of those working with rhesus monkeys is that the latent period after estrogen-progesterone treatment is shorter and less variable than that after treatment with estrogen alone. These observations in part have been confirmed clinically by Palmer³ who observed that "although the estrogen withdrawal bleeding interval has been found to be quite constant in patients with primary amenorrhea and natural menopause, this is not the case in women with varying degrees of ovarian function exhibiting normal or abnormal menstrual cycles." Other observations on monkeys indicate that there is no difference in the duration of bleeding or the latent period following different levels of estrogen therapy.⁴ Palmer,⁵ from the study of eight amenorrheic or postmenopausal patients under treatment for a total of 19 cycles, concluded that the latent period was consistent regardless of variations in dosage and of methods of administration. Lastly, it was shown in monkeys that the duration of bleeding is longer after estrogen-progesterone treatment cycles than after estrogen treatment cycles.^{3, 4}

For a number of years, patients have been treated in the Endocrine Division for functional disturbances of uterine bleeding with various schedules of cyclic, oral steroid therapy.⁶ Analysis of the treatment data of some of these patients provides considerable information on the character of the latent period and on the duration of bleeding following estrogen and estrogen-progesterone oral therapy.

Method of Study

The material of this study concerns 276 cycles of 86 patients. For purposes of statistical analysis the patients were divided into four groups according to their history of bleeding:

- Group 1. Patients with irregular, profuse and prolonged uterine bleeding.
- Group 2. Patients with cyclic, profuse and prolonged uterine bleeding.
- Group 3. Patients with infrequent and scanty uterine bleeding.
- Group 4. Patients with absence of uterine bleeding for at least a year (amenorrhea), or failure of occurrence of menarche.

*Part of the expenses incurred in these studies was defrayed by grants to one of us (E.C.H.) from Ayerst, McKenna, and Harrison, Ltd., New York, N. Y. and from the Research Council of Duke University.

It is clear that radical vulvectomy is applicable to a much larger proportion of patients than has previously been thought possible. Many of these are poor surgical risks and one does not dare to give them prolonged general anesthesia. It is our conclusion that the main feature in allowing wide applicability is the relative safety of the local anesthesia.

As to preparation, we do nothing locally to prepare for the operation. The tumor cannot be sterilized. We are dealing with an essentially infected area and cannot avoid it. Preoperative sulfonamides and penicillin have not been effective. All these patients carry retention catheters, and it has been our practice to use penicillin starting immediately after operation and add sulfonamides as soon as the urinary output has been established at 1,000 c.c. in twenty-four hours.

The preparation for local anesthesia is important. We begin sodium amytal preparation well ahead of time. The patient is given 6 grains of sodium amytal three hours before operation. One and one-half hours later the patient is seen and, depending upon the age and size of the patient and the estimated degree of sensitivity to barbiturates, another 3.0 grains of sodium amytal may be given. Hyosine, $\frac{1}{150}$ grain, is given when the patient is called to the operating room. Two-thirds of the patients have no memory of the operation. They wake up and wonder why the dressing is on. It is necessary to reinject with anesthetic solution under direct vision when the sensitive areas of the inguinal and femoral canals and the region of the clitoris are exposed. Occasionally extra morphine or demerol is given during operation.

The postoperative care involves the usual things. We use pressure dressings and we get the patients up and walking the day of operation.

ysis failed to reveal any difference, and, in all further calculations, the type of estrogen used was disregarded.

Duration of the latent period; variation with different hormone schedules: The data are presented graphically in Fig. 1. In this section the character of the disturbance requiring treatment was not considered. It is evident that the patients treated with E+P bleed much sooner than those treated with E alone. This difference is statistically significant. The profound effect exerted by progesterone is illustrated by the following figures. The mean latent period with cyclic E is 5.4 days, whereas that with cyclic E+P is 2.7 days. With *estrogen alone* only 28.5 per cent of patients bled within the first four days and 68.9 per cent started to bleed between the fourth and eighth days.

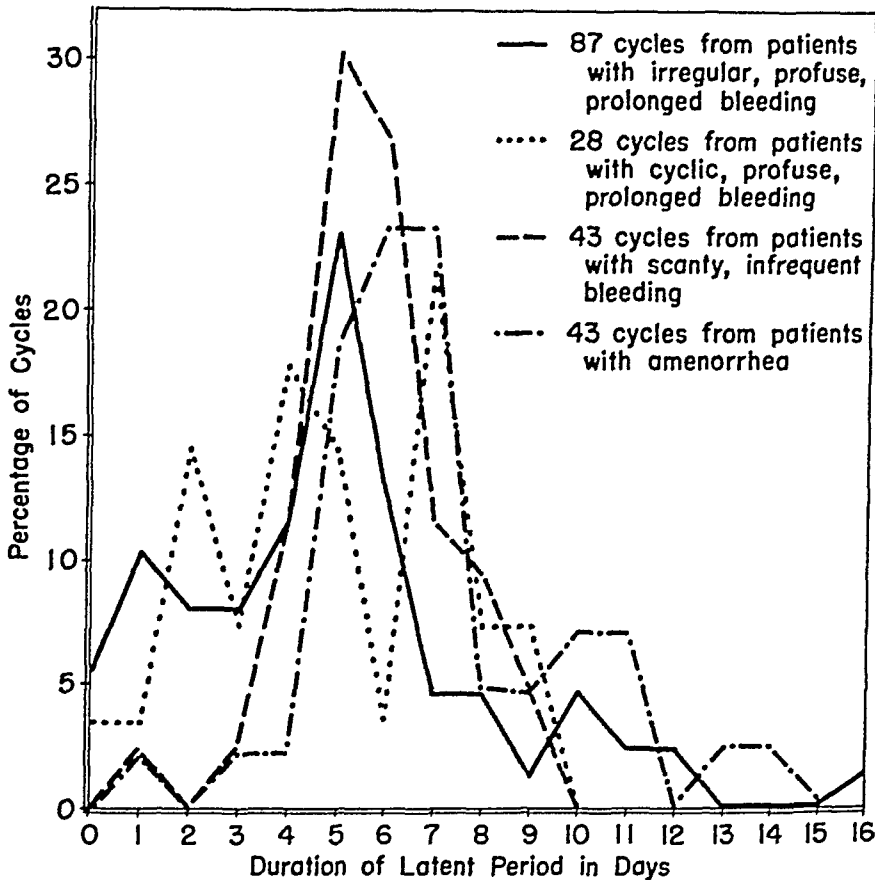


Fig. 2.—Duration of the latent period following cyclic estrogen therapy, and the influence of the type of functional disturbance under treatment.

Ninety-five and seven-tenths per cent had started to bleed within the first ten days after estrogen withdrawal. By comparison, 84.4 per cent of patients started to bleed within four days after the end of E + P therapy (74.4 per cent within three days) and in only 23.4 per cent did bleeding start between the fourth and eighth days. Ninety-six and one-tenth per cent started to bleed within six days after the end of treatment.

There is some difference (not statistically significant) between the curves of patients treated with cyclic E and double E. This difference concerns the height of the curve and not its general shape. This may be explained in part by the fact that double E was given usually during the first cycle of treatment. It is, of course, less likely that these first attempts at cyclic regulation should yield as homogeneous data as do subsequent cycles. This has been shown previously by one of us (E. C. H.).⁶

Several therapeutic schedules were employed:

1. Cyclic estrogen therapy consisting of the daily oral administration of 3.75 mg. of conjugated estrogens (premarin) or 3.0 mg. of diethylstilbestrol from the fifth to the twenty-fifth day of the cycle. Henceforth this will be referred to as cyclic E treatment.

2. Daily administration of 7.5 mg. premarin or 6.0 mg. of diethylstilbestrol from the fifth to the twenty-fifth day of the cycle. This will be referred to as double-E therapy.

3. The administration of 3.75 mg. of premarin or 3.0 mg. of diethylstilbestrol daily from the fifth to the twenty-fifth day of the cycle and 30 mg. of anhydrohydroxyprogesterone (pranone) daily from the fifteenth to the twenty-fifth day of the cycle. This will be referred to as E + P therapy. In a few instances, double-E + P also was used.

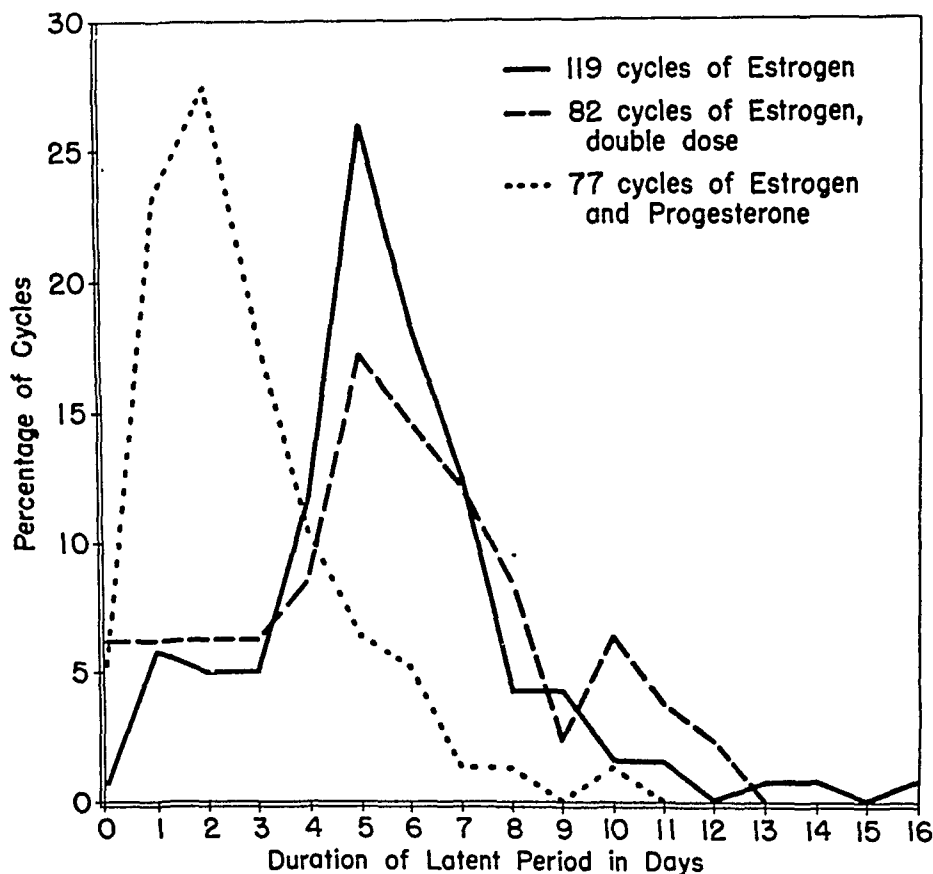


Fig. 1.—The effect of cyclic estrogen or estrogen and progesterone on the duration of the latent period.

The various correlations of latent period and of the duration of bleeding to the type of treatment and to the nature of the functional disorder then were plotted and analyzed for their statistical significance. In these calculations all cycles in which breakthrough bleeding occurred during treatment or bleeding failed to occur after therapy were excluded.

Results

Choice of estrogen: It was important to determine at the very beginning of this study whether or not the choice of natural (premarin) or synthetic (diethylstilbestrol) estrogen made any difference in the data. Statistical anal-

curve is explained by the fact that this was usually the first cycle of treatment and, accordingly, effects of the previous functional disturbance persisted. The mean duration of bleeding of patients treated with cyclic E was 5.2 days; 83.1 per cent bled from three to seven days. With double E the mean duration was 5.5 days and 78.2 per cent from three to seven days. With E + P the mean duration was 5.4 days and 89.3 per cent bled for three to seven days.

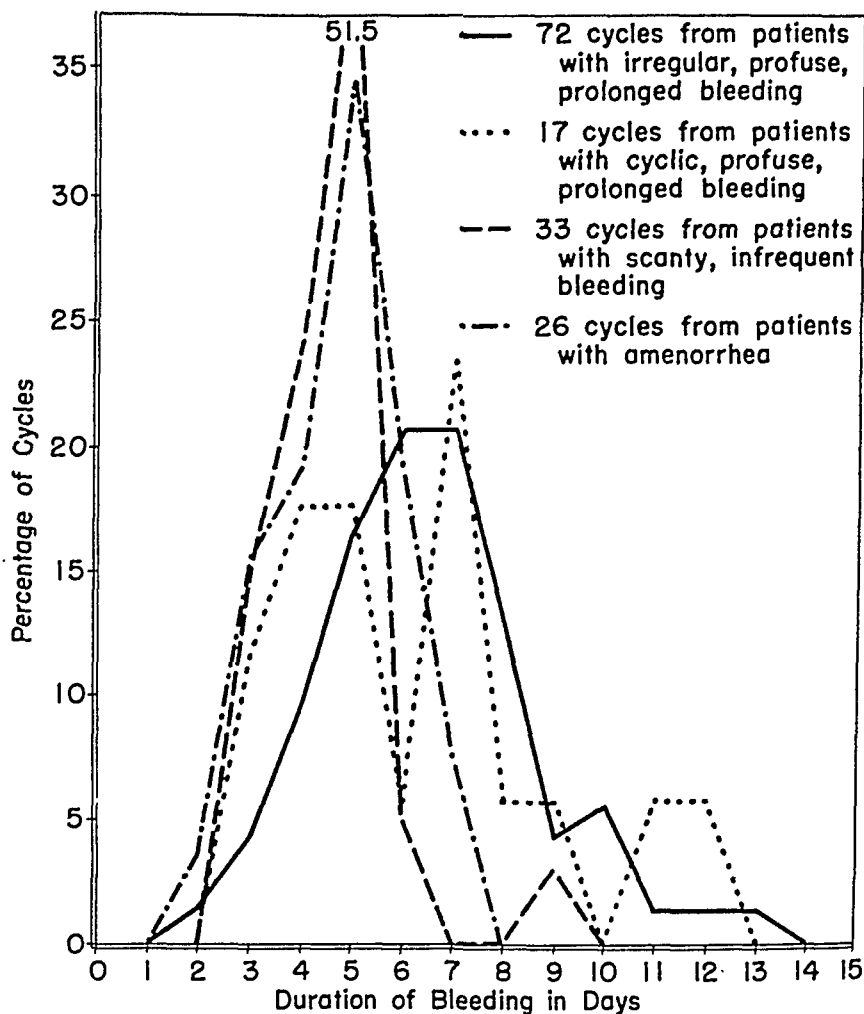


Fig. 4.—Duration of uterine bleeding following therapy, and the influence of the type of functional disturbance under treatment.

Duration of bleeding; variation with the character of the functional disturbance: The entire group of patients is included in these calculations (Fig. 4) inasmuch as it was shown that the duration of bleeding was unaffected by the treatment schedule (i.e., whether E or E + P). The curves show clearly that those patients treated for excessive bleeding continue to bleed for relatively longer periods than those patients who originally had infrequent and scanty or absent periods before treatment. Those patients under treatment for irregular excessive bleeding and for cyclic excessive bleeding bled for a mean of 6.5 and 6.3 days, respectively. Bleeding lasted for three to six days in 51.4 per cent of the former group and in 53.0 per cent of the latter group. By way of contrast patients under treatment for infrequent scanty bleeding and for amenorrhea bled for a mean of 4.6 and 4.7 days, respectively. Bleeding lasted for three to six days in 96.9 per cent of the former and in 88.5 per cent

Duration of latent period; variation with the character of the functional disturbance: It is obvious from the foregoing section that the E and E+P groups cannot be considered simultaneously when studying the latent period. There were not enough E+P cycles available in each subgroup, based on the nature of the functional disturbance, to yield statistically significant data. Therefore, only those patients treated with cyclic E and double E are considered. Fig. 2 presents these data. The irregularity of the curves, in large measure, is due to the relatively small number of cycles available for study.

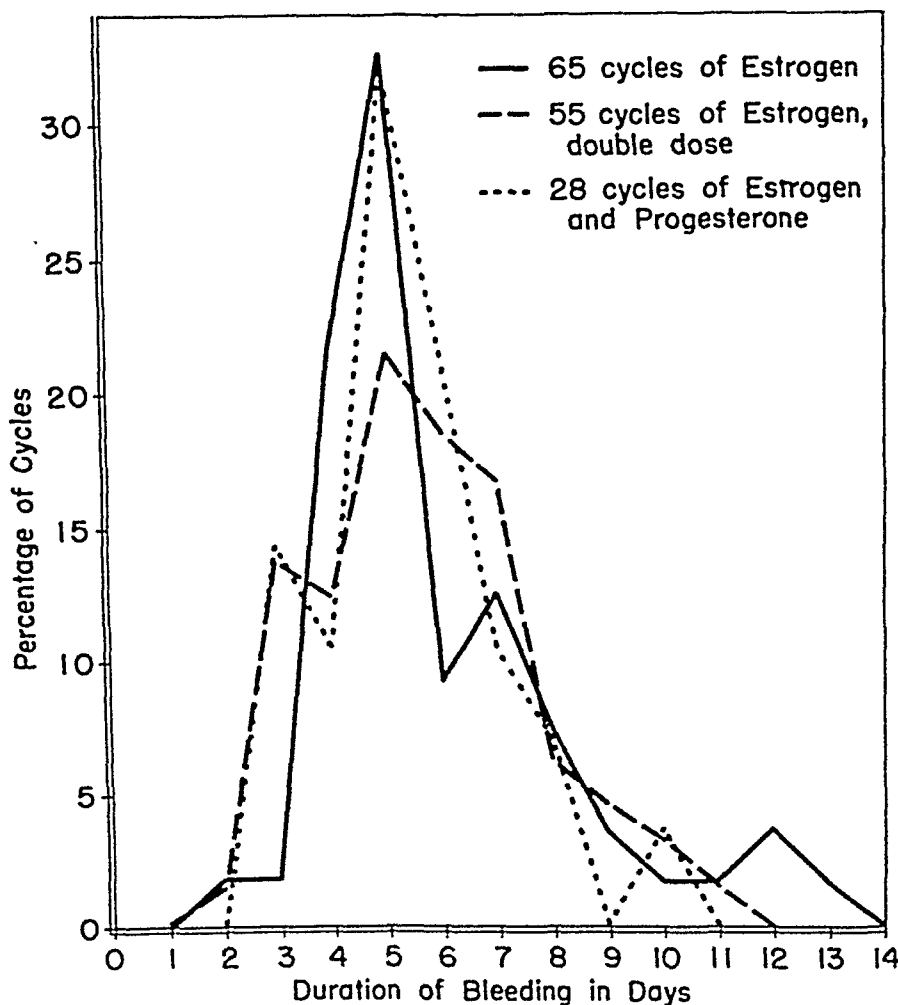


Fig. 3.—The effect of cyclic estrogen or estrogen and progesterone on the duration of uterine bleeding.

For this reason, frequency distribution figures, for the most part, were not statistically significant. One important feature is observed, however: 43.5 per cent of patients with irregular excessive bleeding and 46.4 per cent of patients with cyclic excessive bleeding had a latent period of four days or less following estrogen therapy. These data contrast with those of patients with infrequent scanty bleeding and amenorrhea, of whom only 16.4 per cent and 6.9 per cent respectively bled within the 4 days after the withdrawal of treatment. These data are statistically significant.

Duration of bleeding; variation with different hormone schedules: These data are presented in Fig. 3. The addition of progesterone to the treatment did not increase the length of the period of bleeding, contrary to observations on experimental animals. The slightly different appearance of the double-E

Harrison, Ltd., New York, New York. Anhydrohydroxyprogesterone (pranone) was supplied for these studies by Schering Corporation, Bloomfield, New Jersey.

This present study would not have been possible were it not for the exact and conscientious records kept by past members of the department.

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of the latter group. Statistical analysis confirms the unquestionable significance of these figures despite the relatively small number of cycles available in each group.

Discussion

Our data bear out observations in monkeys that the latent period after estrogen-progesterone treatment is shorter than that after estrogen treatment alone. On the average, the latent period was 2.7 days (50 per cent) shorter in the E+P group. On the other hand we did not find that the duration of bleeding was prolonged by the administration of anhydrohydroxyprogesterone, as it has been observed with progesterone by Cleveland¹ and Phelps.⁴ It is possible that this difference resulted from the use of castrated animals.

Forty-three cycles of estrogen therapy were studied in patients with amenorrhea or failure of occurrence of menarche; the duration of bleeding was relatively constant but the latent period was not. Essentially similar observations were made on the group with infrequent scanty bleeding.

We were able to corroborate the statement of Palmer³ that the method of administration did not have any effect on the nature of bleeding. In comparing our results from oral E+P therapy with similar schedules of E+P given parenterally which have been published elsewhere,⁷ identical curves for the duration of bleeding were obtained. Our observations on the similarity of results following E and double-E therapy confirm the statements of Phelps⁴ and Palmer⁵ that there is no difference in latent period or duration of bleeding with different levels of adequate estrogen therapy.

Conclusions

1. The latent period after cyclic estrogen-progesterone therapy is shorter (mean 2.7 days) than after cyclic estrogen therapy alone (mean 5.4 days).
2. Patients under treatment for functional excesses of bleeding, bleed more promptly after estrogen withdrawal (43.5 per cent to 46.4 per cent in four days) than do those under treatment for infrequent scanty bleeding or amenorrhea (6.9 per cent to 16.4 per cent in four days).
3. Even under cyclic hormone therapy (E or E+P), patients with excesses of bleeding tend to bleed longer than those with infrequent scanty or absent periods.
4. Progesterone does not prolong the duration of bleeding in women treated for functional uterine disturbances.
5. Doubling the dose of estrogen did not affect the latent period or duration of bleeding.
6. The duration of bleeding is identical when estrogen-progesterone is given orally or parenterally.
7. The choice of synthetic (diethylstilbestrol) or natural (premarin) estrogen did not influence the latent period or duration of bleeding.

We express indebtedness to Dr. Donald S. Martin, Professor of Public Health and Preventive Medicine, for assistance in the statistical treatment of the material. Estrogens (premarin and diethylstilbestrol) were supplied for these studies by Ayerst, McKenna and

but most of these patients were suffering from backache. From the psychological and practical standpoint, we feel that these patients must be considered in labor and treated as such.

Material Studied

In the four-year period between July 1, 1942, and June 30, 1946, 5,599 patients were delivered at the Lewis Memorial Maternity Hospital, the Obstetrical Teaching Unit of the Loyola University Medical School. Of these, 224 (or 4.00 per cent) patients had labor exceeding twenty-four hours' duration, and hence classified as prolonged labor cases. The cases excluded obstructed labor due to complicating tumor or disproportion, and were confined to those instances in which normal progress would be expected but which did not materialize. We feel, in accord with the findings of Calkins¹ and Murphy,² that presentation and position do not materially influence the first stage of labor in the majority of the cases. They do however, play a more important part in the second stage and its management; hence we have included the cases of brow, breech and transverse presentations in our figures.

Management

The patients were for the most part handled by the resident staff under the direct supervision of the senior staff member in charge of the prolonged Labor Service in accordance with our established routine. The routine procedure is based on extreme conservative management directed toward anticipating and combating infection and exhaustion during the antepartum phase, and maintaining a constant vigil for hemorrhage and shock during the postpartum phase.

As it is an established fact that the incidence of infection is increased as the duration of labor is lengthened, particularly after the rupture of the membranes, rectal and vaginal examinations are kept to a minimum. Every effort is made to avoid vulval contamination during rectal examinations, and all vaginal examinations are made in the delivery room under strict aseptic technique.

We attempt to combat dehydration, starvation, and exhaustion by the early institution of a dietary regime which includes small feedings of a soft diet every four hours. Liquid intake by mouth is encouraged. In the event that the patient is unable to retain food or liquid by mouth, 1,000 c.c. of a 5 per cent glucose in saline solution is administered twice a day or oftener, if indicated. Exhaustion is combated by an eight-hour period of rest alternating with a like period of labor. Morphine sulfate was the drug of choice in these cases as the barbiturates not infrequently caused excitation in the patient.

When labor has been in progress for twenty-four hours, the urine is examined every six hours for acetone and albumin and the fluid output checked carefully. In the event of the appearance of acetone and di-acetic acid in the urine, with a rising pulse rate and signs of impending collapse, the patient is heavily sedated and placed on continuous fluids. With the proper early treatment and management, we feel that the danger of collapse is minimal.

During the period following the sedation the labor usually progressed without stimulation. In few instances, intravenous calcium gluconate, quinine, and rarely small doses of pituitrin were used. The majority received no artificial stimulation.

Delivery was not attempted in any case until the first stage was terminated and the cervix completely dilated. Major operative procedures were discouraged during the second stage unless the conditions and indications warranted interference.

THE MANAGEMENT OF PROLONGED LABOR

A Four-Year Review From the Lewis Memorial Maternity Hospital

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ONE of the most trying complications of pregnancy confronting the obstetrician is the management of prolonged labors. The designation prolonged labor is an arbitrary one and each investigator has his own criterion. Cosgrove and Glisson² set thirty-six hours as the limits of normal labor. Douglas and Stander³ in their study of *Infantile Mortality in Prolonged Labors* used thirty hours as the limit. Kuder and Johnson⁴ also used thirty hours in their study on *The Elderly Primipara*. On the other hand, Williams,¹³ in his analysis of the 206 maternal deaths associated with prolonged labor, and Linn and Douglas,⁵ in their treatise on *Prolonged Labor*, defined as prolonged any labor exceeding twenty-four hours' duration. We, too, have selected twenty-four hours as the limit of normal labor.

Further complicating the criterion of prolonged labor is the difficult differentiation between the so-called "false pain" and the "true pain." Patients may enter the hospital with apparently severe pain only to have the pain disappear entirely and the true labor not occur until several weeks later. On the other hand the patient may have "false pains" which may suddenly change to "true pains." Still further adding to the confusion is the factor of individual differences in the evaluation of labor pain by the various physicians or the residents examining the patients. These factors make any determination of the length of labor in a large series merely an estimate which cannot be entirely accurate.

Notwithstanding the variable and uncertain criteria for classification, the group of patients designated as "prolonged labor cases" poses a real problem in its management. If the attendant yields to the pleas of the patient or her family and attempts an ill-advised interference, he may do irreparable damage to her future chances of conceptions, and perhaps leave her in a state of chronic invalidism as well as further jeopardizing the mother and the infant in this present pregnancy.

Definition.—In this investigation, twenty-four hours has been selected as the limit beyond which the labor is considered prolonged. Labor was considered to be initiated with the onset of regular uterine contractions associated with pain, regardless of the presence or absence of effacement, dilatation of the cervical os, or the rupture of the membranes.

On estimating the duration of labor, we necessarily counted the elapsed time from the onset to the delivery. In the majority of the longer cases, there were some periods in which the patient was not having regular contractions.

*Read before the Chicago Gynecological Society, Jan. 17, 1947.

plications encountered are shown in Table IX. Table X describes the morbidities encountered during the series. There were 22 morbid cases, or 9.9 per cent as compared with an over-all morbidity of 3.8 per cent. Table XI shows the prenatal complications met with in this group. Table XII compares the infant mortality in the group of prolonged labor cases with the total infant mortality in all cases delivered. It is significant that there is a marked rise in the percentage of infant mortality in the prolonged labor group.

Among the 5 599 cases delivered in the four-year period, 35 were elderly primiparas—that is, women 35 years or older who were delivered of viable infants for the first time. The age ranged from 35 to 42 years. The duration of labor varied from 5 hours, 4 minutes to 107 hours and 20 minutes with an average of 17½ hours. Seven delivered spontaneously, 11 were delivered by

TABLE VII. TYPE OF DELIVERY

| | | |
|---|----|-------|
| Spontaneous | 54 | 24.1% |
| Outlet forceps | 82 | 35.6% |
| Low forceps | 58 | 25.8% |
| Mid forceps | 8 | 3.5% |
| Breech | 10 | 4.4% |
| Breech extraction | 8 | 3.5% |
| Version and extraction | 3 | 1.3% |
| Manual correction of brow, low forceps | 1 | 0.4% |
| Forceps correction of brow, rotation and extraction | 1 | 0.4% |

TABLE VIII. CONDITION OF PERINEUM AND CERVIX FOLLOWING THE DELIVERY

| | I | II | III | IV | V | VI | VII | VIII | IX |
|--|-----|----|-----|----|---|----|-----|------|---------|
| Intact | 1 | 5 | 6 | 3 | 3 | 2 | 2 | 1 | 1 |
| Episiotomy | 146 | 19 | 6 | 3 | 1 | 0 | 0 | 0 | 0 |
| Episiotomy with Cervical laceration | 3 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| 1° Laceration | 3 | 1 | 2 | 0 | 1 | 0 | 0 | 0 | 0 |
| 2° Laceration | 0 | 2 | 0 | 2 | 0 | 2 | 0 | 0 | 1 |
| 2° Laceration \bar{c} Cervical laceration | 1 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 |
| 2° Laceration \bar{c} Para-ureth. laceration | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 3° Laceration \bar{c} Cervical laceration | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Laceration of Vaginal wall | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 155 | 29 | 16 | 9 | 6 | 4 | 2 | 1 | 2 - 221 |

TABLE IX. COMPLICATIONS OF LABOR AND DELIVERY

| | |
|--|----|
| Contraction ring | 1 |
| Intrapartum infection | 1 |
| Maternal exhaustion | 11 |
| Uterine inertia | 12 |
| Deep transverse arrest of the head | 19 |
| Persistent occiput posterior | 18 |
| Prolapsed cord | 2 |
| Transverse lie with prolapsed cord | 1 |
| Intrapartum hemorrhage | 2 |
| Postpartum hemorrhage | 14 |
| Postpartum hemorrhage and shock | 2 |
| Chill immediately postpartum | 1 |
| No FHT at onset of labor | 3 |
| Epileptic seizures during labor | 1 |
| Fetal distress | 2 |
| Vaginal bleeding due to placenta previa marginalis | 1 |
| Postpartum shock | 1 |
| Abruptio placenta | 1 |

Following delivery, the patient is kept in the delivery room under sterile drapes for a period of one hour. The blood pressure is checked every fifteen minutes or oftener if indicated. Early use of plasma and whole blood are encouraged. Intrauterine packs are used to control hemorrhage when needed, but such procedure tends to increase the danger of infection.

Results

The results of our study are depicted on Tables I to XII. Table I shows the cases grouped into twelve-hour periods from twenty-four to one hundred and eight hours and the relative frequency of each period. In Table II the distribution is according to age, and in Table III according to parity. It is significant that the primigravidas represent the majority of the cases. Table IV further subdivides the primigravidas into age group. In Table V is shown the position and presentations encountered. In this grouping, we find that 164 cases presented as occiput anterior, 18 as persistant occiput posterior, and 19 as deep transverse arrest. Table VI gives the classification of the type of pelvis based on the impression and measurements of the examining physician. Table VII is self-explanatory, and describes the types of delivery encountered. Table VIII reveals the damage to the perineum and cervix in this series. The com-

TABLE I. LENGTH OF LABOR

| DURATION IN HOURS | 24-36 | 37-48 | 49-60 | 61-72 | 73-86 | 87-96 | 97-108 |
|-------------------|-------|-------|-------|-------|-------|-------|--------|
| Number of cases | 140 | 50 | 20 | 7 | 5 | 1 | 1 |
| Percentage | 62.5% | 22.3% | 8.9% | 3.1% | 2.2% | 0.44% | 0.44% |

TABLE II. AGE DISTRIBUTION

| AGE GROUPS | 16-19 | 20-29 | 30-39 | 40-45 |
|-----------------|-------|-------|-------|-------|
| Number of cases | 27 | 141 | 47 | 9 |

TABLE III. DISTRIBUTION BY GRAVIDITY

| GRAVIDA | I | II | III | IV | V | VI | VII | VIII | IX |
|-----------------|-----|----|-----|----|---|----|-----|------|----|
| Number of cases | 155 | 29 | 16 | 9 | 6 | 4 | 2 | 2 | 1 |

TABLE IV. AGE DISTRIBUTION OF THE PRIMIGRAVIDAS

| AGE GROUPS | 16-20 | 21-25 | 26-30 | 31-35 | 36-45 |
|-----------------|-------|-------|-------|-------|-------|
| Number of cases | 36 | 59 | 39 | 12 | 9 |

TABLE V. PRESENTATIONS AND POSITIONS

| CEPHALIC | BREECH | OTHERS |
|----------|---------|----------------|
| OLA - 93 | LSA - 7 | Transverse - 1 |
| OLT - 6 | LST - 2 | Brow - 2 |
| OLP - 8 | LSP - 2 | RMA & RMT |
| ORA - 71 | RSA - 7 | |
| ORT - 13 | RST - 1 | |
| ORP - 10 | RSP - 1 | |

TABLE VI. "CLINICAL" CLASSIFICATION OF PELVIS

| | |
|--------------------------------|-----|
| Normal gynecoid | 207 |
| Gynecoid with android tendency | 10 |
| Slightly platypelloid | 3 |
| Platypelloid | 4 |
| | 224 |

Discussion

In reviewing the present series, we find that our incidence of 4.0 per cent compares favorably with Williams' incidence of 4.70 per cent, Huber's Chicago Lying-in incidence of 6.3 per cent and Cosgroves' Margaret Hague Maternity Hospital incidence of 5.9 per cent.

The causes of prolonged labor may be divided roughly into two groups: (1) those causing prolongation of the first stage of labor, and (2) those causing prolongation of the second stage. As Calkins¹ has pointed out, the first stage is involuntary and has to do only with the cervical effacement and dilatation, whereas the second stage is at least partly voluntary and has to do with the propulsion of the fetus through the birth canal.

In this series, we found that the incidence of prolonged second stage was very low, about 5 per cent of the cases having a second stage lasting over three hours. Operative interference, of course, is responsible for the shortening of the second stage in a large percentage of the cases, so that we have no way of determining how many more might have occurred.

The prolongation of labor is usually due to the prolonged first stage. The duration of the first stage is dependant on two main factors: (1) resistance of the cervix to dilatation, and (2) the all-important intensity and frequency of the labor pain. We do not feel that the position, the presentation, the size of the fetus, or the station of the presenting part are primarily the cause of prolongation of the first stage. It is our impression that a faulty and ineffectual type of pain is usually responsible. This is in accord with the findings of Murphy's work with the Lorand tocograph, which verified the conclusion of Calkins and others.

Prolonged labor due to cervical dystocia is usually due to congenital anomaly, severe scarring from previous trauma, or longstanding infections with resulting fibrosis or scarring. It is generally conceded by most writers however, that cervical dystocia alone is seldom the cause of prolonged labors. Cosgrove, in 1939, directed our attention to the infrequency of cervical dystocia requiring Dührssen's incision, and our experience with this group of cases tend to bear out his finding, as we had no instance in which cervical incision was considered to be indicated. His over-all fetal mortality of 7 per cent coincides closely with our own uncorrected fetal mortality of 7.4 per cent.

In our group of elderly primiparas, although the number is too small for an adequate statistical study, it would seem that age presents a definite factor in the ability of the uterus to develop a vigorous type of contraction. Over 25 per cent of the group from 36 to 42 years of age developed prolonged labor.

Termination of prolonged labor by cesarean section carries a very high maternal mortality, as shown by Williams¹³ in his analysis of 206 deaths in prolonged labor. In the event that this procedure be required, he recommends the Waters type of operation as being the least hazardous for the mother.

Conclusions

1. Prolonged labor is usually the result of an ineffectual type of uterine contractions.

TABLE X. MORBIDITY

| | |
|--|----|
| Mild endometritis | 1 |
| Endometritis | 1 |
| Endometritis and myometritis | 1 |
| Thrombophlebitis | 1 |
| Acute congestive mastitis | 2 |
| Pyelitis | 1 |
| Cystitis | 1 |
| Paralytic ileus | 1 |
| Intestinal obstruction | 1 |
| Infected episiotomy | 1 |
| Infected episiotomy & breakdown of wound | 2 |
| Abscessed tooth with cellulitis | 1 |
| Upper respiratory infection | 2 |
| Infected thrombosed hemorrhoids | 1 |
| Pyelocystitis | 3 |
| Unknown etiology | 2 |
| | 22 |

TABLE XI. PRENATAL COMPLICATIONS

| | |
|---|---|
| Mild hyperemesis gravidarum | 2 |
| Hyperemesis gravidarum | 2 |
| Mild hypertensive toxemia | 9 |
| Hypertensive toxemia | 7 |
| Marked varicosities of legs and vulva | 2 |
| Sinus arrhythmia | 1 |
| Rheumatic heart disease | 1 |
| Epilepsy | 2 |
| Cystitis | 1 |
| Pyelitis | 1 |
| Lues | 1 |
| Gastritis | 1 |
| Chaneroid | 1 |

TABLE XII. INFANT MORTALITY

| | | | |
|------------------------------|-------------|--|------------|
| Total number of deliveries-- | 5599 | Total number of prolonged labors | 224 |
| Total infant mortality incl. | | Total infant mortality incl. Prematures | 16 (7.40%) |
| Prematures | 146 (2.60%) | Fetal deaths | 5 (2.23%) |
| Fetal deaths | 64 (1.14%) | Stillbirths | 11 (4.91%) |
| Stillbirths | 82 (1.46%) | Corrected mortality | (6.69%) |
| Corrected mortality | (1.66%) | | |

outlet forceps, 9 by low forceps, 3 by forceps rotations with low forceps extraction, and 5 elective cesarean sections of the low cervical type were performed. In this group of elderly primiparas, 9 (25.7 per cent) were cases of prolonged labor. Their ages ranged from 36 to 39 years. The duration of labor was 26½ hours to 107 hours, 20 minutes, with an average of 47 hours, as compared to the average length of 37.8 hours in the whole series of prolonged labor. The complications of pregnancy, labor, and types of delivery have already been indicated on the tables.

In the entire group of elderly primiparas (35 patients), the infant mortality totaled five cases (16 per cent), three fetal deaths, one of which was premature, and two stillbirths. It is interesting to note that four out of the five deaths occurred in cases of prolonged labor. In other words in nine cases of prolonged labor in women 35 years or older, 4 had dead babies (44 per cent) while in the remaining 26 cases there was only one stillbirth.

There was no maternal death in this series of 224 cases of prolonged labor.

centimeters dilated, and the head well in the pelvis with no progress for six to eight hours, in spite of apparently adequate uterine contractions. I believe it is less traumatic to both the mother and the child to terminate labor at that time than to allow her to go on an indefinite number of hours with the outcome still uncertain. These conditions when Dührssen's become necessary are relatively rare, but they do arise.

It is to be noted that in any unselected consecutive series of cases the incidence of cesarean sections would be much higher than these cited by Dr. Bremner, who had exactly none. This is indeed a compliment to his obstetric skill and judgment. At the same time I would like to point out that of the sixteen babies who did not survive, four occurred in his nine cases of elderly primigravida, those who could least afford to lose their child. If these deaths occurred during labor one might conjecture that these are the cases in which a cesarean section may have been indicated.

I should like to emphasize an excellent point Dr. Bremner brought out in his paper, and that is the extremely high incidence of postpartum hemorrhage following a prolonged labor. His series contained six cases, an incidence of 7 per cent, a fact which we should be cognizant of and be prepared to handle if necessary.

In conclusion, I would like to recommend, besides the sedation and parenteral fluids Dr. Bremner mentioned during labor, the use of vitamin K to the mother and the baby soon after delivery as well as the use of chemotherapy, especially if the membranes have been ruptured for any length of time.

DR. DAVID N. DANFORTH.—Dr. Bremner mentioned the use of calcium for purposes of stimulation in prolonged labor. I should be interested to know of his results with this therapy. In our experience calcium is of value only in selected cases, where all of the mechanical requirements for normal labor are fulfilled. It is not useful in cases where inertia can be ascribed to faulty fitting of the presenting part to the lower uterine segment, or as is often found in malposition or malpresentation, or where inertia may be due to improper alignment of the uterus to the pelvis. Where factors such as these cannot be demonstrated, calcium appears to be useful.

DR. BREMNER (Closing).—In regard to determining when labor actually begins, I pointed out that we are very much convinced that we must consider these cases psychologically in labor, even though there is no effacement or cervical dilatation. I realize that there is great controversy and difference of opinion in this matter. I neglected to include that in practically all of these cases vitamins were added to the medication.

Concerning Dührssen's incision, it so happened that we did not have any. Possibly there were cases in which that might well have been used. I personally rarely use Dührssen's incisions, I do not like them. That is probably why they were not done. We sectioned 35 per cent of our primigravidas that were over 35 years of age. The other primiparas that were not sectioned were those that we expected up to a certain stage would deliver normally, and after that we could not do cesarean section without producing maternal morbidity or increasing the risk of maternal mortality. I agree that psychiatric factors probably play a greater role than we now give them credit.

I believe it was Eastman who recommended small doses of pituitrin. He believed it stimulated uterine contractions and definitely improved his results. My own personal results with pituitrin are not good. I have had two cases in the past ten years that developed tetanic contractions.

Our success with intravenous calcium gluconate was extremely variable, so much so that we could not come to any accurate determination. It was used symptomatically, depending on the response. We do not have much to say either for or against it.

2. There is a definite increase of fetal mortality in prolonged labor.
3. The morbidity rate is increased in patients which are in labor more than twenty-four hours.
4. The elderly primipara group shows a higher percentage of prolonged labor than the younger group.
5. The elderly primipara group in prolonged labor shows a marked increase in the fetal mortality over the younger age group.

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Discussion

DR. HENRY BUXBAUM.—I believe Dr. Bremner is erroneous on his assumption that his figures are comparable to those of Williams, Huber, and Cosgrove, inasmuch as he has utilized a different standard. In the first place he eliminated all cases of prolonged labor due to disproportion, which is a somewhat difficult thing to do, and, secondly, I would like to question his definition for the onset of labor. It has always been my opinion that labor is not considered initiated until there is some effacement and or dilatation of the cervix. The pains prior to this time may be considered as preliminary according to Hamilton. Therefore the similarity of the incidence of prolonged labor (4 per cent) between his figures and those cited is more apparent than real. Prolonged labor is beyond a doubt the most difficult complication to handle in the entire field of abnormal obstetrics and requires keen observation and sound judgment. When a situation such as this does arise it behooves the obstetrician to re-evaluate the case thoroughly. As to the mother, her pulse, temperature, blood pressure, pelvic architecture, and general physical condition. As to the fetus, position, presentation, size, attitude, station, and heart tones. And also as a means to determine what we can expect the woman to accomplish herself, we must resort to some one of the impression methods as Munro-Kerr, Mueller, or Hillis, or your own personal modification of one of these three methods. Dr. Bremner stated that, in his opinion, ineffectual uterine contractions are responsible for most cases of prolonged labor. This undoubtedly is true, but I do not believe we can entirely divorce this factor from two other closely related factors, namely, anomalies of the passages and anomalies of the passengers. As a matter of fact, he has an incidence of 10 per cent breech presentations in his series, besides 18 occiput posteriors, 1 transverse presentation, and 1 brow presentation. Many times, unfortunately, in my experience, not one, but all these factors are present to add to the difficulties of the obstetrician.

I agree with Dr. Bremner in his condemnation of the use of barbiturates in these cases. He uses morphine sulfate, we use demerol, both opiates. Barbiturates do not give the patient the necessary rest or relaxation, and renders her incapable of cooperating when this is most necessary.

I do not understand Dr. Bremner's hesitancy to perform Dührssen's incisions when indicated. Especially in a primigravida with the cervix completely effaced, more than seven

Type of Delivery.—Table I shows the incidence of methods of delivery, while Figs. 1 and 2 show their annual variations. During the last five years, considerable change has occurred in the obstetric routine. Low forceps delivery, our method of choice, has shown a steady increase (Fig. 1).

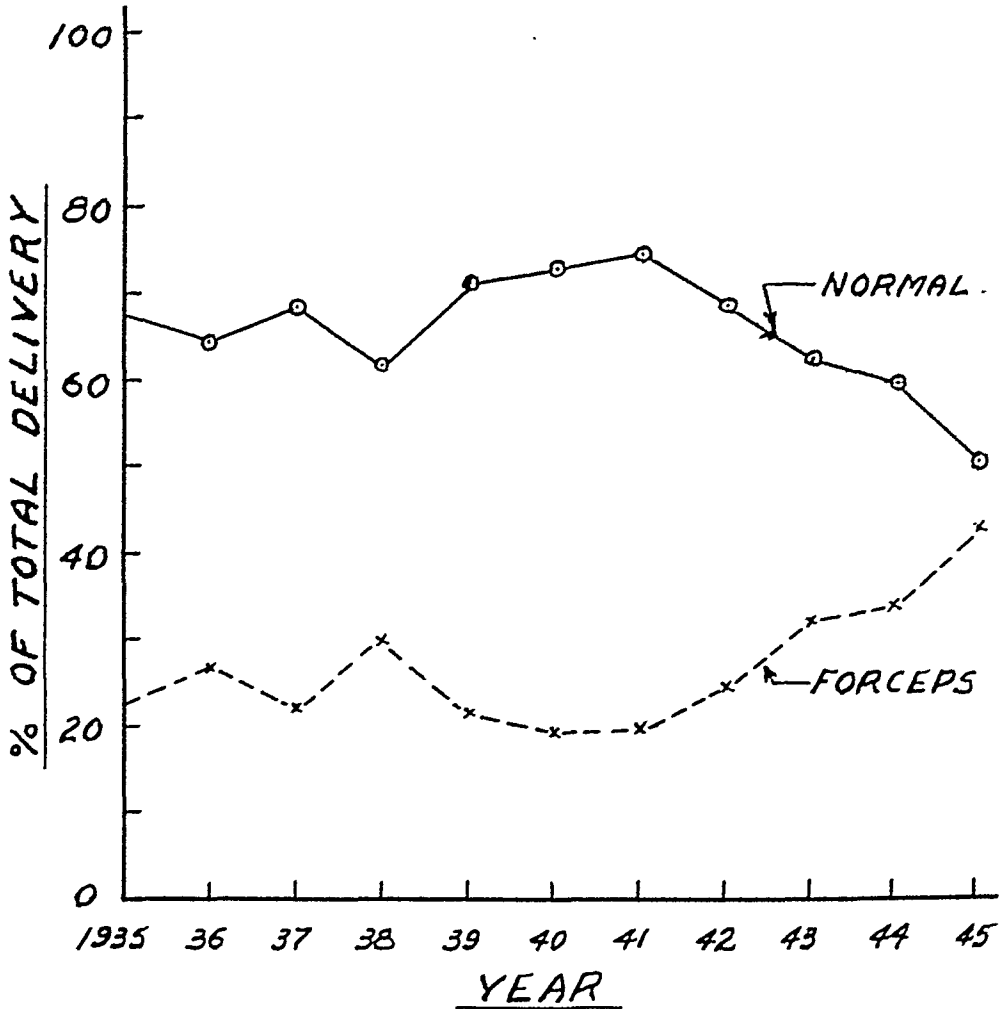


Fig. 1.—Relative incidence of normal and forceps delivery.

TABLE I. TYPE OF DELIVERY

| TYPE OF DELIVERY | NUMBER OF CASES | PER CENT |
|-------------------|-----------------|----------|
| ✓ Normal (vertex) | 9,825 | 65.14 |
| Forceps | 4,282 | 28.38 |
| Breech | 656 | 4.34 |
| Cesarean section | 205 | 1.35 |
| Version | 120 | 0.79 |
| Total | 15,088 | 100.00 |

TABLE IA. TYPE OF FORCEPS DELIVERY

| TYPE | NUMBER OF CASES | PER CENT |
|--------|-----------------|----------|
| High | 222 | 5 |
| Middle | 852 | 20 |
| Low | 3,208 | 75 |
| Total | 4,282 | 100 |

FETAL AND MATERNAL MORTALITY*

An Eleven-Year Survey

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ALTHOUGH great advances have been made in the practice of obstetrics in the past decade, there remains much room for improvement in procedure.

Stander,³ in his vehement appeal for unification of obstetric and gynecologic teaching, pleaded for better instruction in obstetric practice in our schools of medicine. In this regard, one of his more pertinent arguments was the statement: "The family doctor usually does not practice surgery, and most frequently has time to consult another physician or internist. On the other hand, he invariably delivers women and cares for the ills of women. Thus he assumes a great responsibility in the lives of both mother and child." This statement is corroborated by the fact that the majority of women are delivered by general practitioners, who lack an adequate obstetric training. Surgeons, moreover, have invaded the pregnant uterus, performing cesarean section with doubtful indications and high maternal mortality.

For these reasons, we consider Stander's appeal opportune, and it is our purpose to show, by analysis of local figures, that observance of proper obstetric practice is a major means of improving obstetric results.

Material and Methods

This paper represents a compilation of the data collected in a survey covering an eleven-year period from January, 1935, through December, 1945, at the Department of Obstetrics, Bethesda Hospital, Cincinnati, Ohio. About 80 per cent of the patients were delivered by private physicians. The remaining 20 per cent are "service" patients and were delivered by interns and residents under the supervision of members of the obstetric staff.

In this study, only patients who were delivered in the hospital were included. Excluded also was a small group of patients whose pregnancies were interrupted prior to five months' gestation. These, for one reason or another, had not been admitted to the gynecologic service.

Although the main purpose of this study was the analysis of maternal and fetal mortality rates, we found it of interest to scrutinize the incidence of the various modes of presentation and the types of delivery. In order to obtain a clear conception of the variation in mortality, in relation to the degree of the physician's obstetric experience and training, the deliveries performed by obstetric specialists and general practitioners were separately listed.

During the eleven-year period, 15,088 patients were delivered. It is interesting to note that in the last three years (1943 to 1945) this rate was three times that of 1935. This emphasizes the great increase in the number of hospital versus home deliveries in recent years.

Incidence of Presentation.—Vertex presentation comprised 95 per cent of the total, and breech 4.4 per cent. Face, transverse, and brow presentations, respectively, comprised the remainder of these cases.

*Presented at a meeting of the Cincinnati Obstetrical Society, Oct. 17, 1946.

mainder by obstetricians.* It has been the policy of the Obstetrical Committee of this hospital to insure the ready availability of expert consultation for general practitioners and their patients at all times. As a result, a steadily increasing number of general practitioners' cases, especially the abnormal ones, have had the benefit of consultative advice from one or another member of the obstetric staff. Deaths, fetal or maternal, which occurred in cases in which the consultation of an obstetric specialist had been obtained, were included in the mortality figures of the latter group.

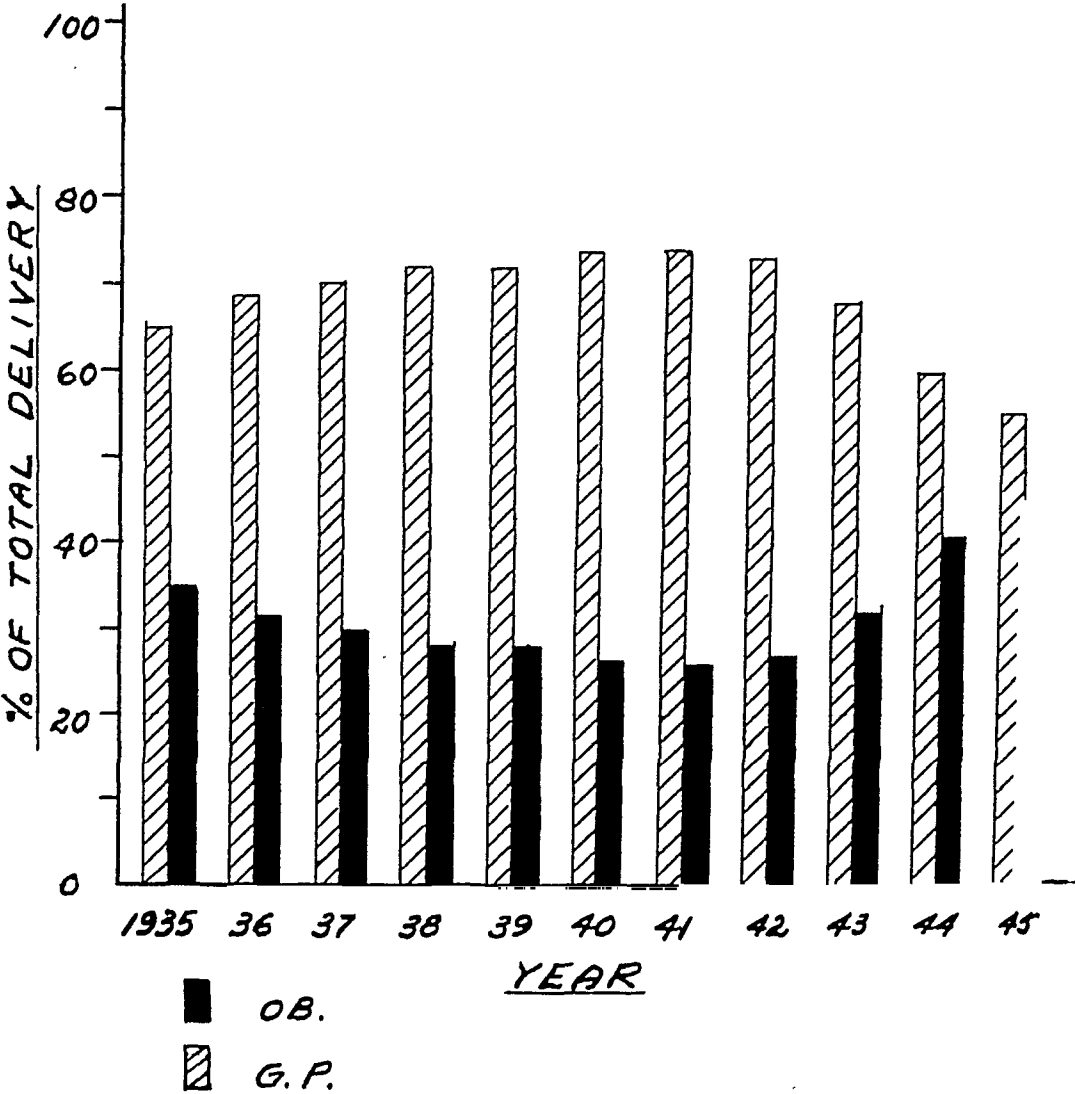


Fig. 3.—Annual variation of obstetricians' and general practitioners' work.

Fig. 3 shows that the percentage of deliveries performed by obstetricians has been steadily increasing in the last few years. It is possible that this was a contributory factor in the decrease of maternal and fetal mortality in this hospital during the same period.

Fetal Mortality.—Of 15,088 deliveries, 2.68 per cent were stillborn, and 1.82 per cent were neonatal deaths, comprising a gross mortality rate of 4.50 per cent. However, if we exclude the instances of macerated fetuses and congenital abnormalities incompatible with life, the average corrected mortality

*In the former figures are also included the deliveries performed by residents and interns, even though they were supervised by members of the obstetric staff.

The most striking changes were observed in the annual rate of section and high forceps. Between 1935 and 1940, 85 per cent of the cesarean sections were performed by general surgeons in collaboration with general practitioners. In 55 per cent of these operations, the generally accepted criteria for cesarean sections were not demonstrated. In 1940, the Obstetrical Committee ruled that no section or high forceps delivery could be performed by any practitioner or surgeon without previous consultation with a qualified obstetrician. This important decision resulted in a steady decline in the number of deliveries by these two methods. In the last four years the average percentage of cesarean sections was reduced from 3 per cent to approximately 0.65 per cent. This

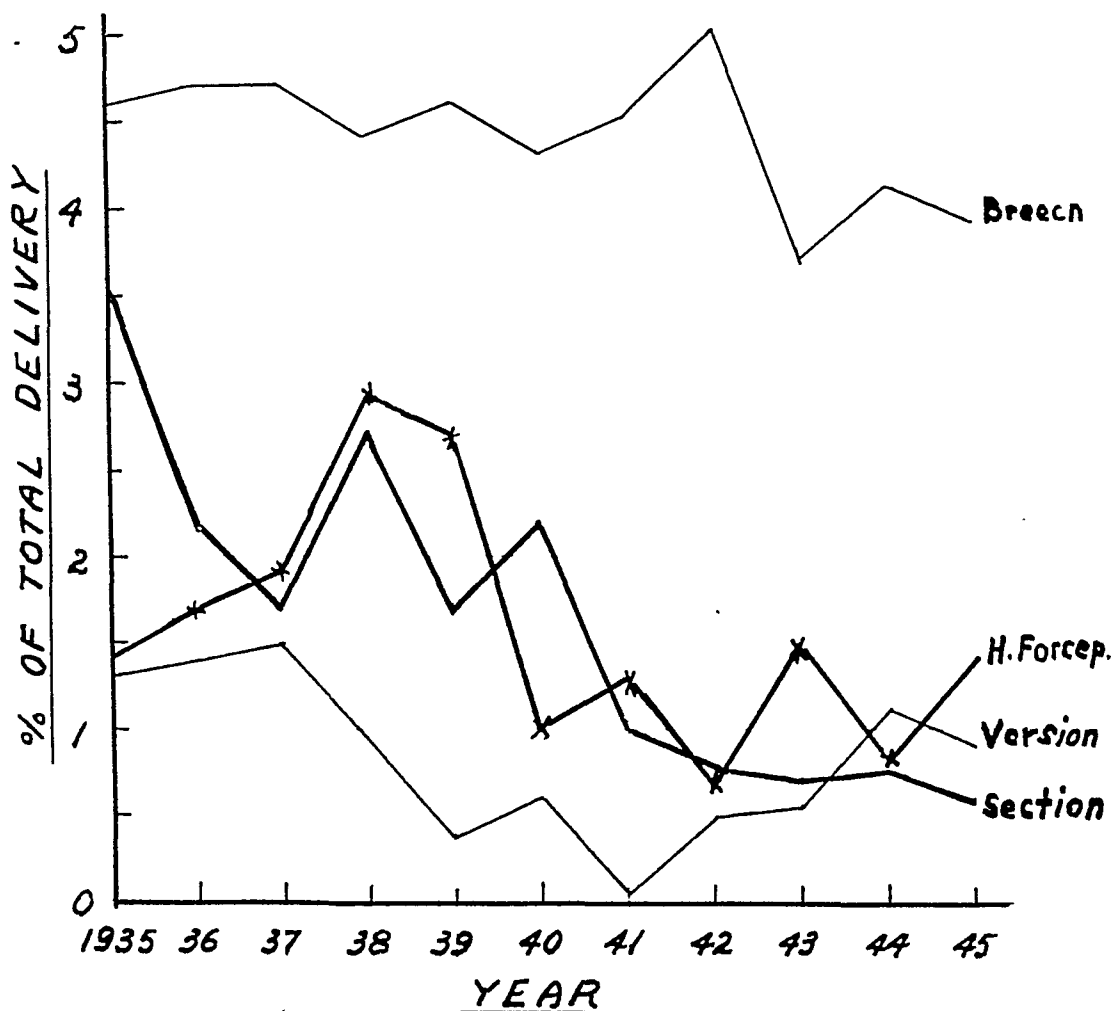


Fig. 2.—Relative incidence of breech, section, high forceps, and version delivery.

constitutes the smallest incidence that we have ever observed here, and it is much lower than the average incidence reported by other authors.^{4, 6, 14} During the same period, almost all of the cesarean sections were performed by obstetricians. Cephalopelvic disproportion constituted the major indication. Central placenta previa and a very limited number of cases of toxemia and premature separation of placenta were also treated by cesarean section.

High forceps application which was included in the same ruling showed a similar decrease in utilization, as evidenced in Fig. 2.

Obstetricians' and General Practitioners' Work.—Of the total number of deliveries, 67 per cent were performed by general practitioners, and the re-

TABLE II. FETAL DEATHS

| TYPE OF DELIVERY | TOTAL DELIVERY | STILLBORN | | NEONATAL DEATH | |
|------------------|----------------|-----------|----------|----------------|----------|
| | | DEATHS | PER CENT | DEATHS | PER CENT |
| Normal | 9,825 | 215 | 2.19 | 159 | 1.62 |
| Forceps | 4,282 | 71 | 1.66 | 48 | 1.12 |
| Breech | 656 | 73 | 11.10 | 41 | 6.24 |
| Version | 120 | 30 | 25.00 | 14 | 13.70 |
| Section | 205 | 13 | 6.34 | 13 | 6.34 |
| Total | 15,088 | 402 | 2.68 | 275 | 1.82 |

mortality rate. Although these figures are in disagreement with those reported by Irving,¹⁴ we feel justified in minimizing the use of high and mid-forceps, but retaining the use of low forceps as a method of choice.

Breech and internal version delivery had the highest mortality rate. The uncorrected mortality for breech delivery was 17.35 per cent. Although high, it can be compared favorably with figures reported in other series.⁸ Dieckmann,¹³ in a very careful analysis of breech mortality, stated that it ranges from 3.8 per cent to 52 per cent. His own uncorrected mortality of 7.7 per cent is a proof of real improvement in breech delivery.

The management of breech presentation and its major problems have been outlined by Dieckmann.¹³ It is our belief that this presentation should always be considered, particularly by the general practitioners, as a potential danger to the child, and any improvement in its handling will certainly reduce the fetal mortality.

The elevated mortality rate of internal version is a clear indication that its use should be relegated to the experienced obstetrician and then only in carefully selected cases.

TABLE III. FETAL DEATH RELATIVE TO OBSTETRICIAN AND GENERAL PRACTITIONER

| TYPE OF DELIVERY | STILLBORN | | | | NEONATAL DEATH | | | |
|------------------|----------------------|----------|--------------|----------|----------------------|----------|--------------|----------|
| | GENERAL PRACTITIONER | | OBSTETRICIAN | | GENERAL PRACTITIONER | | OBSTETRICIAN | |
| | DEATH | PER CENT | DEATH | PER CENT | DEATH | PER CENT | DEATH | PER CENT |
| Normal | 168 | 41.80 | 47 | 11.70 | 127 | 46.20 | 32 | 11.60 |
| Forceps | 48 | 11.92 | 23 | 5.90 | 28 | 10.15 | 20 | 7.26 |
| Breech | 47 | 11.60 | 26 | 6.40 | 25 | 9.10 | 16 | 5.82 |
| Version | 16 | 3.97 | 14 | 3.48 | 8 | 2.90 | 6 | 2.25 |
| Section | 7 | 1.74 | 6 | 1.49 | 12 | 4.36 | 1 | 0.36 |
| Total | 286 | 71.03 | 116 | 28.97 | 200 | 72.71 | 75 | 27.29 |

Table III shows the comparative fetal death rate relative to obstetricians and general practitioners. Of the total fetal deaths, 72 per cent were attributed to general practitioners, and the remaining 28 per cent to obstetricians. On the other hand, it should be emphasized that obstetricians managed more complicated cases and were called in consultation only after difficulties had arisen. Nevertheless, if we take into consideration the relative proportion of the total number of deliveries performed by general practitioners and that performed by obstetricians, it is quite evident that the highest incidence of infant loss occurred in the hands of the former group.

Premature Infant Mortality.—The criteria which have been adopted by several authors,⁷⁻⁹ in studying premature infant mortality, are based on the weight and length of the baby. Unfortunately, we were not able to utilize this method since the weight and length of a large number of stillborn infants were

would be 3.5 per cent. This incidence is high compared to 2.14 per cent reported by De Lee and Greenhill²; 2.67 per cent by Stander³; and 2.63 per cent by Beck.⁹ It could be, however, favorably compared to 4.0 and 4.50 per cent, which is the average incidence occurring in all the hospitals of Illinois,⁶ Ohio,¹² and a collected series from hospitals in Chicago.⁶⁻⁸

Fig. 4 shows the annual variation of both gross and corrected mortality rates. During the last four years there was a slight improvement in the fetal mortality. These figures confirm Stander's³ contention that, despite the increasing number of hospital births and of mothers receiving prenatal care, the fetal mortality remains disappointingly high.

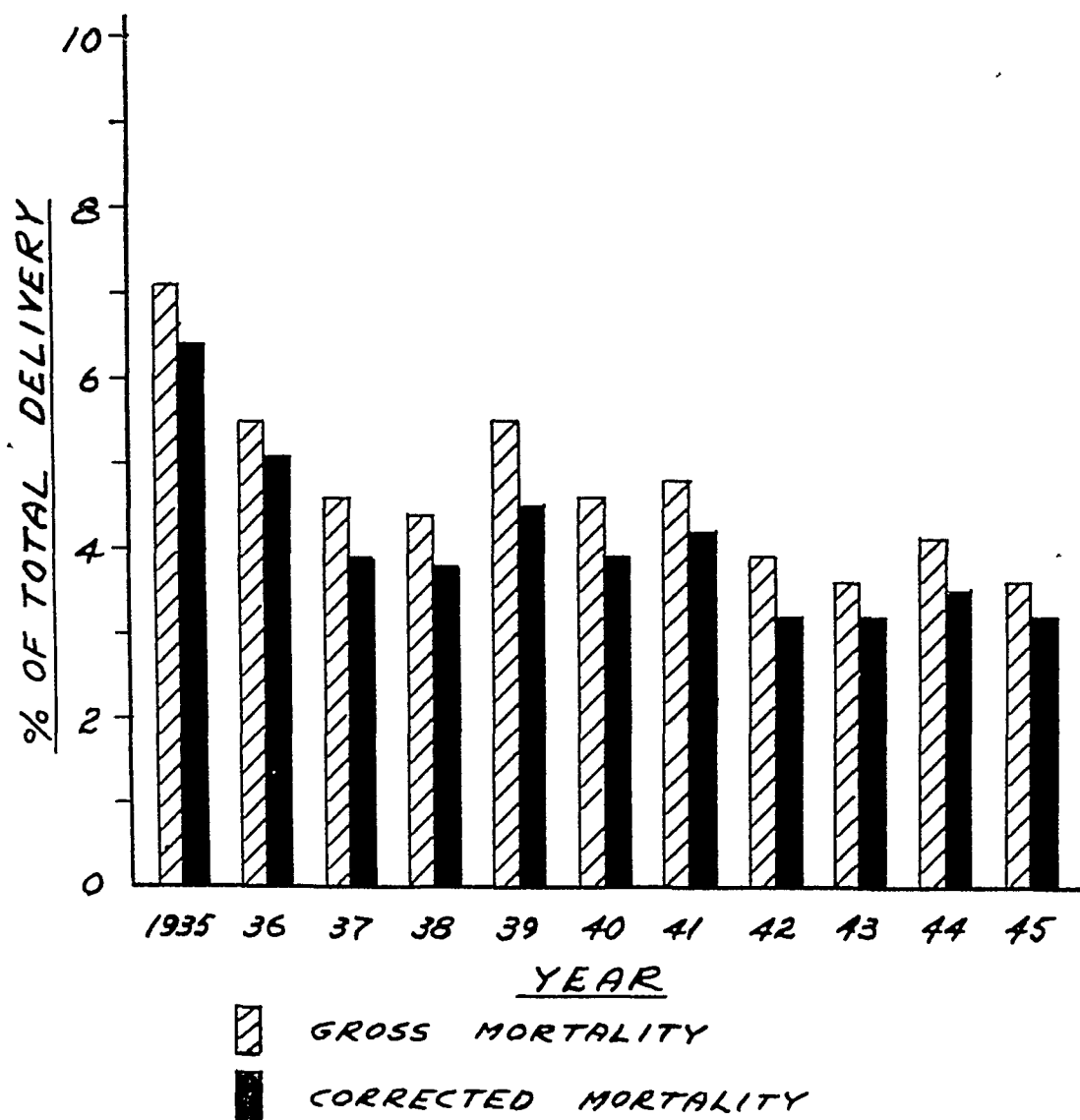


Fig. 4.—Annual infant mortality rates (includes stillborn and neonatal death).

Table II shows the gross infantile mortality relative to each type of delivery. The lowest incidence of fetal death occurred in forceps delivery; 1.66 per cent of the stillborn and 1.12 per cent of the neonatal deaths were the over-all mortality for the three major types of forceps applications. Of these, one-third occurred in high forceps and another one-third in midforceps. If, of the remainder, the cases of macerated fetuses and congenital abnormalities were excluded, then low forceps delivery would have an insignificant

TABLE IV. CAUSES OF INFANT DEATH; FETAL FACTORS

| CLINICAL DIAGNOSES | STILLBORN | | NEONATAL DEATH | |
|---------------------------|-----------|----------|----------------|----------|
| | NUMBER | PER CENT | NUMBER | PER CENT |
| Prematurity | 128 | 31.82 | 134 | 49.50 |
| Macerated fetus | 64 | 15.88 | 0 | 0.00 |
| Intracranial hemorrhage | 30 | 7.46 | 29 | 10.70 |
| Congenital abnormality | 27 | 6.72 | 13 | 4.80 |
| Atelectasis and pneumonia | 26 | 6.48 | 39 | 14.30 |
| Asphyxia | 22 | 5.48 | 4 | 1.48 |
| Unknown | 105 | 26.16 | 52 | 19.22 |
| Total | 402 | 100.00 | 271 | 100.00 |

TABLE V. CAUSES OF INFANT DEATH; MATERNAL FACTORS

| CLINICAL DIAGNOSES | STILLBORN | | NEONATAL DEATH | |
|----------------------------------|-----------|----------|----------------|----------|
| | NUMBER | PER CENT | NUMBER | PER CENT |
| Toxemia | 36 | 8.90 | 6 | 2.21 |
| Premature separation of placenta | 30 | 7.50 | 1 | 0.37 |
| Pro lapse of cord | 24 | 5.96 | 0 | 0.00 |
| Placenta previa | 11 | 2.80 | 7 | 2.58 |
| Rupture of uterus | 3 | 0.74 | 0 | 0.00 |
| No evidence of maternal factor | 298 | 74.10 | 257 | 94.84 |
| Total | 402 | 100.00 | 271 | 100.00 |

TABLE VI. CAUSES OF INFANT DEATH; AUTOPSY FINDINGS

| CAUSE | CASES | |
|-------------------------|--------|----------|
| | NUMBER | PER CENT |
| Intracranial hemorrhage | 20 | 19.80 |
| Congenital abnormality | 16 | 15.85 |
| Atelectasis | 12 | 11.90 |
| Erythroblastosis | 8 | 7.92 |
| Craniotomy | 6 | 5.90 |
| Pneumonia | 4 | 3.96 |
| Asphyxia | 3 | 2.97 |
| Not determined | 32 | 31.70 |
| Total | 101 | 100.00 |

Total deaths (stillborn and neonatal) = 673.

Total autopsy = 101, or 15 per cent of total deaths.

Table IV shows that among fetal factors prematurity was predominant, intracranial hemorrhage second.

Table V shows the maternal factors to which death could be attributed. The major maternal factor proved to be toxemia. The fact that in many of the deaths no evidence of a maternal factor was indicated does not exclude the possibility that one was indeed present. It simply had not been detected or recorded.

Autopsies were performed in 101 of the infant deaths (Table VI). Intracranial hemorrhage was the most frequent positive finding accounting for 20 per cent of the total. In 31 per cent of the autopsies no anatomic cause for death was demonstrated. Our autopsy findings are in close agreement with those of other authors.¹⁻⁸

Maternal Mortality.—During the eleven-year period, 28 maternal deaths occurred, comprising a gross mortality rate of 0.18 per cent. However, from these, two cases can be excluded. The first was a 29-year-old patient, seven months pregnant, who was admitted to the hospital in severe shock following an accidental fall and died a few hours later. The autopsy revealed a trau-

not recorded. Thus, our figures are based on the presumed length of gestation as determined by the attending physician or by the history taken by the house staff.

Fig. 5 shows the premature mortality rate for a five-year period from 1941 to 1945. Of the 146 premature (six to eight months' gestation) babies, almost 75 per cent died. This tremendous mortality constitutes an indication of improper management of premature infants, and it presents a real challenge to both the obstetrician and the pediatrician.

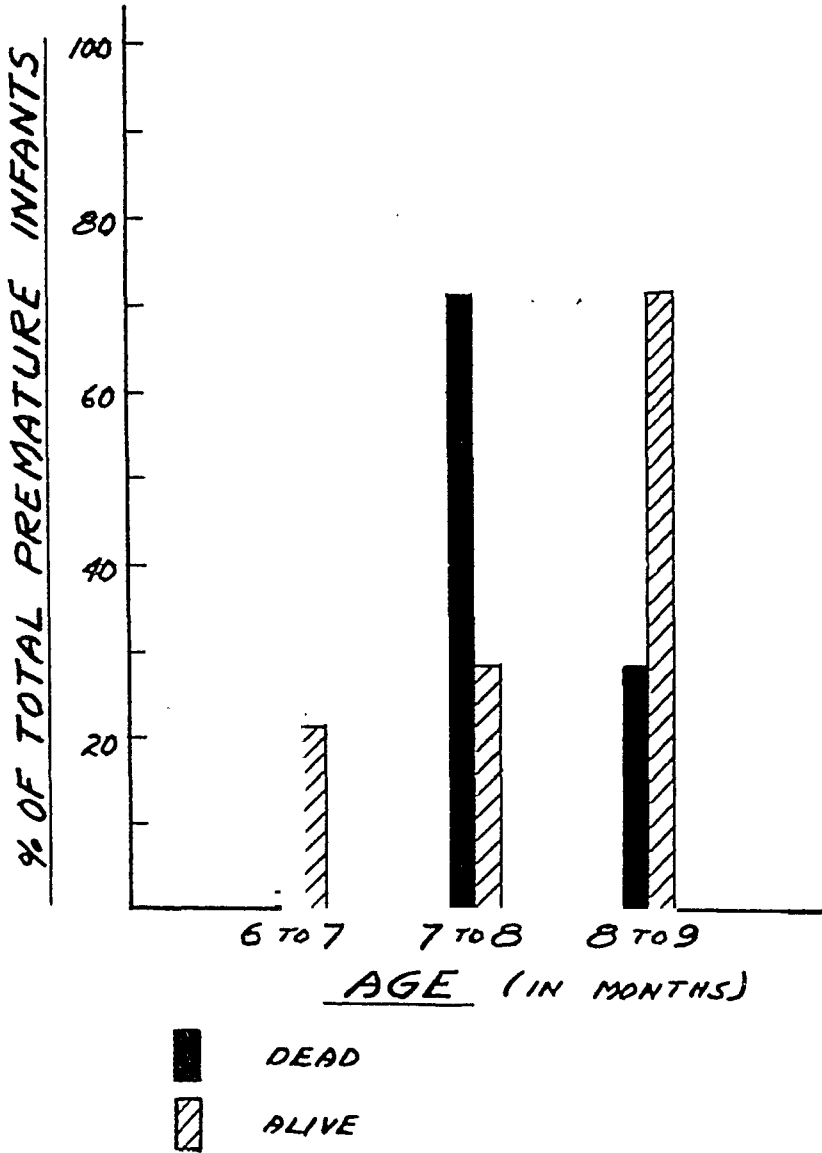


Fig. 5.—Premature infant mortality rates for five-year period from 1941 to 1945, inclusive.

The causes of prematurity and the methods by which the care of premature babies should be carried out have been fully discussed in papers elsewhere.⁷⁻⁹ In this hospital, the highest incidence of prematurity was associated with breech presentation and toxemia. Whether breech presentation is the cause or the effect of premature labor is a subject of controversy.¹¹

Causes of Infant Deaths.—The causes of infant mortality were arbitrarily classified as due to either fetal or maternal factors, although in some cases both factors were concerned.

cent. Although recent papers¹⁻¹⁴ report lower figures for section mortality, it is still generally agreed that this method of delivery is most detrimental to the mother.

TABLE VII. MATERNAL MORTALITY RELATIVE TO TYPE OF DELIVERY

| TYPE OF DELIVERY | NUMBER OF CASES | DEATHS | |
|------------------|-----------------|--------|----------|
| | | NUMBER | PER CENT |
| Normal | 9,825 | 6 | 0.061 |
| Forceps | 4,282 | 5 | 0.117 |
| Breech | 656 | 2 | 0.305 |
| Cesarean section | 205 | 6 | 2.920 |
| Version | 120 | 2 | 1.670 |

Of the total maternal deaths, six cases died before delivery. In two of these, postmortem cesarean section was performed in an unsuccessful attempt to salvage the fetus.

Hemorrhage and shock were the major causes responsible for 28 per cent of the total maternal deaths. Infection caused 25 per cent, toxemia and cardiac disease 18 per cent each, and pulmonary embolism 7 per cent. These figures are more or less in agreement with those reported by other authors.⁵⁻⁶⁻¹⁰

The patients who died of infection had the following clinical diagnoses: peritonitis—one patient; pneumonia—two patients; pyelonephritis—one patient; thrombophlebitis—one patient. It is noteworthy that puerperal sepsis was not a prominent factor. There was only one case of peritonitis which could be directly attributed to puerperal sepsis.

The patients who died of hemorrhage and shock were: rupture of uterus—three patients; placenta previa—two patients; possible uterine atony—one patient; rupture of vagina—1 patient.

Among the total deaths, necropsies were carried out in 15 instances, or 54 per cent. Signs of toxemia and cardiac lesions, mostly of rheumatic origin, were the major postmortem findings.

Comment

In order to have a better understanding of the significance of the figures reported in this paper, it is necessary to divide the eleven years comprising this survey into two periods: the first from 1935 to 1940, and the second from 1940 to 1945.

It is evident that deliveries by general practitioners predominated in the first period. This period was also characterized by abuse of cesarean section, the use of high forceps, and lack of control of the obstetric procedures. In consequence, a high fetal and maternal death rate was noted.

Although obstetricians continued to deliver a relatively small proportion of the cases at the outset of the second period, significant modifications in policy occurred. Rigid rules were established by the Obstetrical Committee regarding the performance of cesarean section and the use of the high forceps. Frequent utilization of obstetric consultants was required, and supervision of the delivery was instituted. These changes brought about definite improvements in standards of practice, with consequent decrease in maternal and fetal mortality. The improvement has been increasingly evident in the latter years of this period.

In the hands of the obstetric staff, breech delivery has received particular attention in recent years. Increasing emphasis on external version and careful roentgenologic study in cases of breech presentation have made possible accurate determination of cephalopelvic disproportion with consequent reduction

matic rupture of the spleen and an aneurysm of the splenic artery. Because this death was not due to pregnancy, it seems reasonable to exclude it. The second case was a 41-year-old patient who was delivered at home and was brought to the hospital in severe shock. She died on the day of entry as a result of multiple lacerations of the vagina with internal and external hemorrhage. Since in our study, home deliveries were not included, this case is likewise deleted. Thus, the over-all maternal mortality was 0.17 per cent, or 1.7 per thousand deliveries.

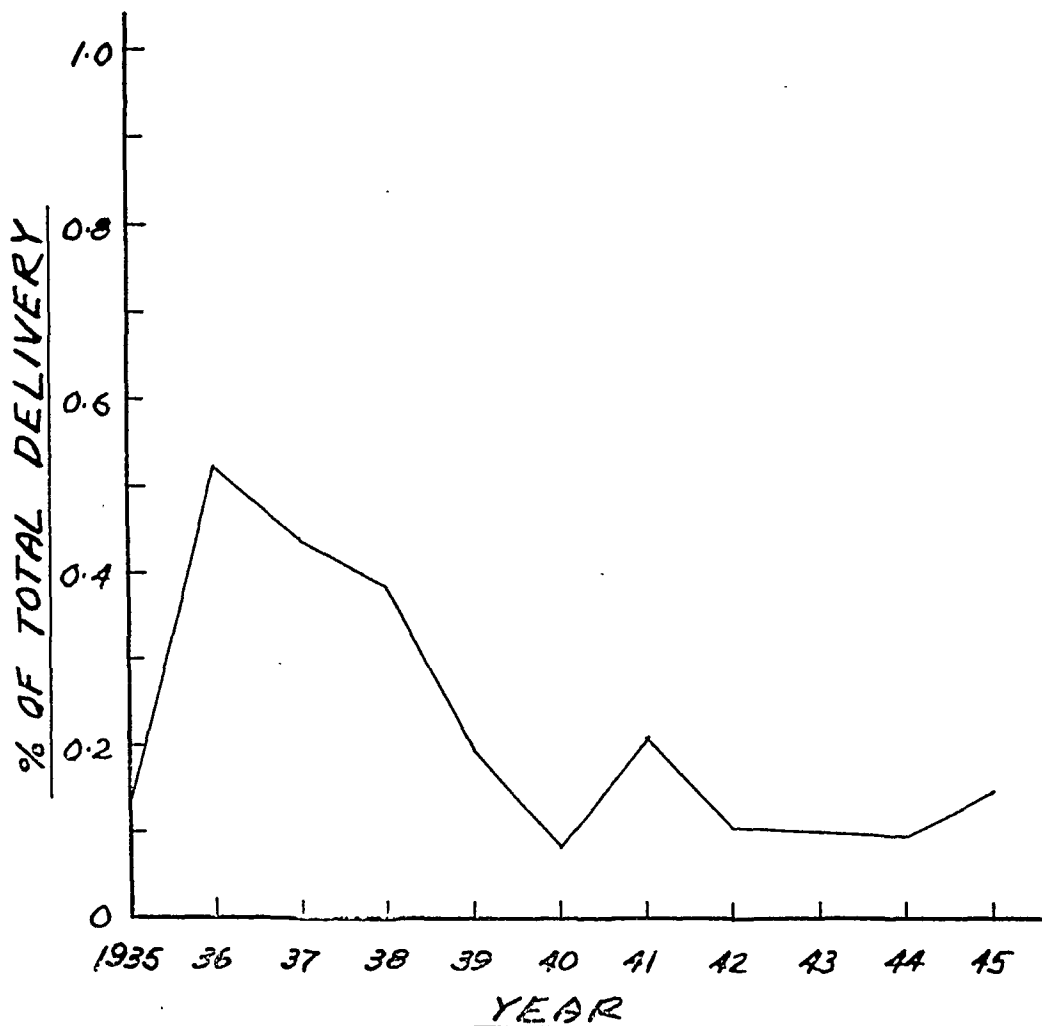


Fig. 6.—Annual maternal mortality rates.

Fig. 6 shows the annual maternal mortality rates. During the last four years it has ranged between 0.10 and 0.13 per cent, which represents considerable progress in the prevention of maternal death. These figures compare favorably with the best results reported by other authors.³⁻⁵⁻¹⁰ In this hospital, the lowered incidence of cesarean section was, undoubtedly, an important factor in the diminution of the maternal death rate, as evidenced by the close parallelism of both curves (Figs. 2 and 6).

Of the 26 cases of maternal death, 19 occurred in the care of general practitioners, and seven in the hands of obstetricians. In two cases included in the latter group, the obstetrician was actually a delayed consultant.

Table VII shows the maternal death rate in conjunction with the type of delivery. Cesarean section had the highest mortality rate, being almost 3 per

A GRAPHIC METHOD OF PROGNOSIS FOR THE INFANT IN THE ANTENATAL CARE OF Rh-ISOIMMUNIZED PREGNANT WOMEN

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BECAUSE of the increased attention to the problem of Rh-isoimmunization in the antenatal care of pregnant women which has generally arisen during the last few years, a method of estimating the prognosis to the fetus, in any one pregnancy, of such women has been sought in this clinic. An extension of this would also apply to subsequent pregnancies.

An analysis of all the cases, 4,569, referred to our Rh laboratory service during 1946 for women whose expected date of delivery was some time in that year, was undertaken, and it was found that when the mother's Rh antibody titer, both agglutinating and blocking,¹ was serially plotted against the weeks of pregnancy, that the graphs fell into five well-defined curves, each an extension of the other. From the results observed of the condition of the babies born to these mothers, together with their subsequent immediate neonatal histories, it became apparent that for each grade of immunization charted the condition of the infants was relatively constant. It is on these results that we feel an accurate forecast can be made of the condition in which the child will be found when born.

Methods Employed

It is now the rule in our Obstetrical Clinics that, when a mother presents herself first for antenatal care, a routine Rh determination is done, after a careful history of previous pregnancies with their outcome, and also of previous transfusions, if any. This serves to eliminate the Rh-positive patients.

If the mother's reading proves to be negative, a few drops of her serum is incubated in a small test tube for an hour with two drops of known Rh-positive cell suspension, against a control. After centrifuging, the serum is decanted and two drops of beef albumin added, and again incubated for one hour.² The results are read as before. In the event of this reading being negative, a note recording that the patient is Rh negative but not yet immunized is made on her antenatal chart, and on each subsequent visit when blood is withdrawn for routine hemoglobin estimation a venous blood sample is set aside and the beef albumin test, outlined above, is repeated. Our usual practice is to see each patient every four weeks during the first trimester, then every three and two weeks during the second and third trimesters, respectively.

However, if at the time of first seeing the patient or at subsequent consultations, the beef albumin test gives a positive agglutination reading, indicating a degree of isoimmunization, a test tube titer is set up using the

in the number of unnecessary cesarean sections. In addition, the use of the bag for dilatation of the cervix and routine episiotomy have made breech delivery less traumatizing.

Despite the continued efforts of obstetricians and pediatricians, little has, as yet, been accomplished in the reduction of mortality attributable to prematurity. It is our hope that by the more extensive employment of the procedures and principles noted concerning breech delivery, plus more circumspect use of maternal sedation, constant use of pediatric consultation and improved management of toxemia, the mortality among premature infants will be reduced.

Summary and Conclusion

1. Fifteen thousand eighty-eight deliveries observed during an eleven-year period have been analyzed (1935-1945).

2. For the entire period, the gross fetal mortality was 4.5 per cent, and the corrected mortality 3.5 per cent. Although it has been improved in the more recent years, these figures still remain high.

3. Breech and version delivery resulted in the highest and low forceps delivery in the lowest fetal mortality rate.

4. Fetal and maternal mortality were higher in the hands of general practitioners than in those of obstetricians.

5. Prematurity was the major fetal contributing factor and toxemia the major maternal factor causing fetal death.

6. The gross maternal mortality was 0.18 per cent, the corrected 0.17 per cent. It has been steadily improved throughout the past few years, during which time it has ranged between 0.10 and 0.13 per cent.

7. Hemorrhage and shock, infection, toxemia, and heart disease were the major causes of maternal deaths.

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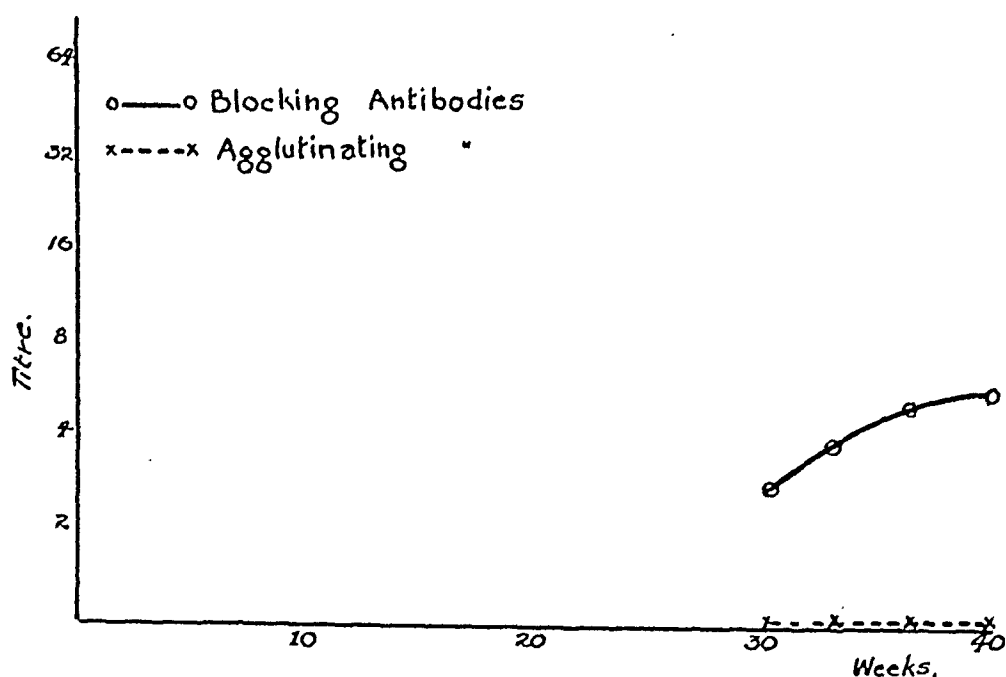


Fig. 2.—Grade II; late appearance of antibodies. Rise in blocking antibodies in the last few weeks of pregnancy not above dilution 1:8. These babies are born at term showing some clinical signs of erythroblastosis of moderate severity. Blood picture at birth confirms this. Infants are usually easily saved by transfusion, etc.

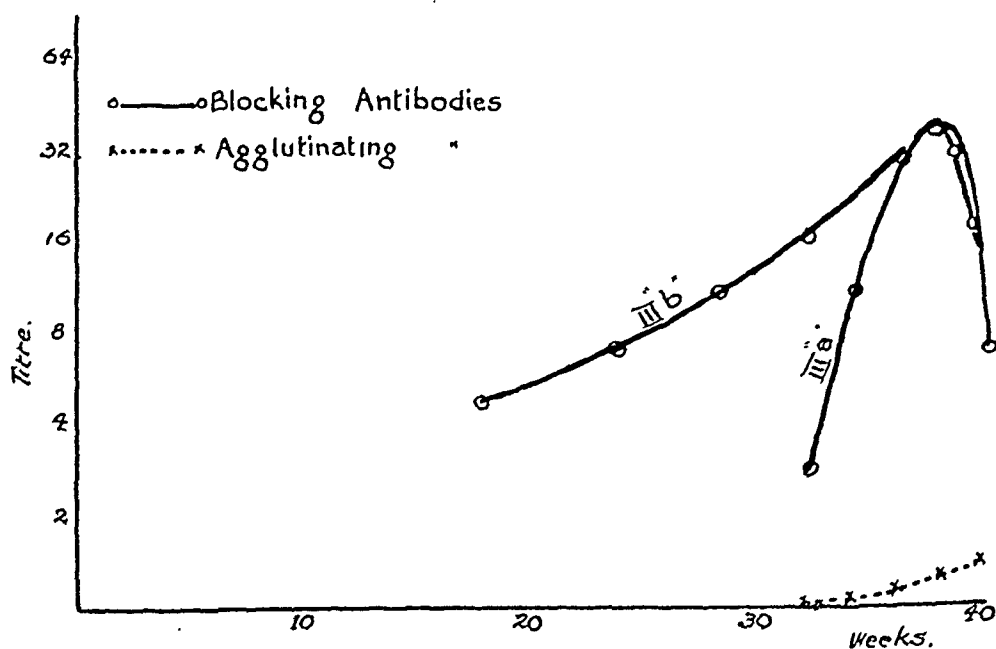


Fig. 3.—Grade III a; a sharp rise in blocking antibodies to dilution 1:32 with often a sudden drop in the last two weeks. Babies severely damaged. May be salvaged by prompt action immediately after birth.

Grade III b; antibodies demonstrable relatively early in pregnancy rising to 1:32 with sometimes a sharp drop in the last two weeks. Prognosis very poor for the baby. Term babies often deadborn.

patient's serum and known Rh-positive cells of various subtypes. Where possible, the husband's blood is also used for this test. The cells are first used in saline suspension in order to demonstrate free agglutinating antibodies; beef albumin being then used to bring out the blocking antibodies. Both these titers are incubated for an hour and read under the low power of the microscope after sufficient centrifuging to pack the cells at the bottom of the tube.

This titer result for agglutinating and blocking antibodies is then charted as shown in Figs. 1 to 5, and the progress of the pregnancy watched carefully by subsequent plotting of titers. The patient may be asked to return for more frequent estimation than is indicated in Figs. 1 to 5 if thought necessary.

Whenever it is possible to obtain a sample of the husband's blood, Rh subgrouping tests are done with a view to detecting whether, if positive, he is homo- or heterozygous. Often with multiple pregnancies and living children it is possible to obtain corroborative evidence of this from Rh testing of the family.

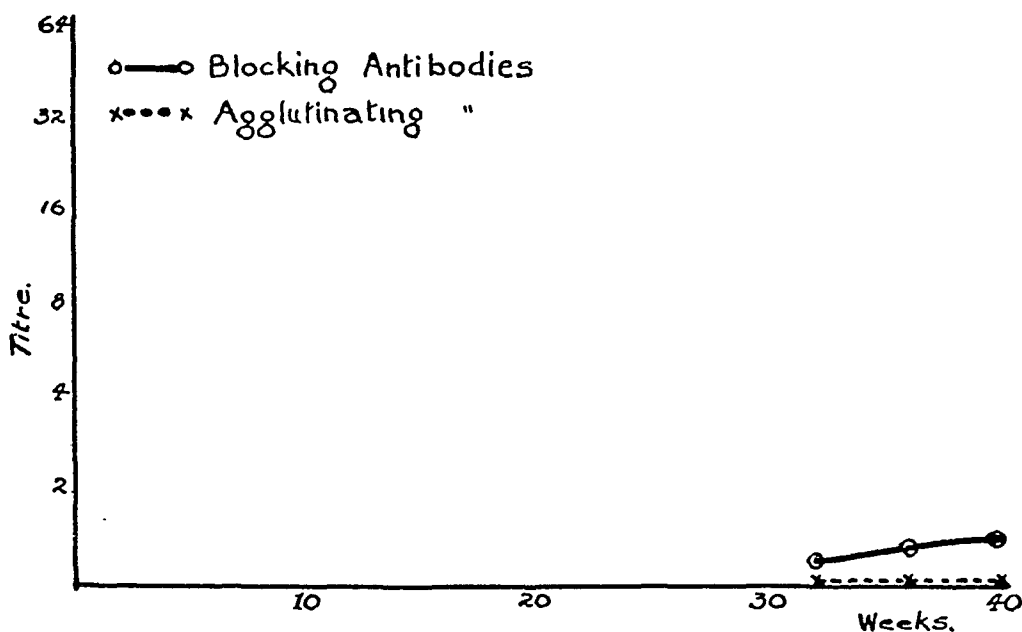


Fig. 1.—Grade I; shows only very slight immunization in later weeks of pregnancy. Babies do well even without treatment in the immediate postnatal period.

Laboratory Results

In the laboratory service attached to the Montreal Maternity Hospital 4,569 preliminary estimations of Rh were done during 1946. Of these, 1,609 were discounted from the results used in this investigation because they were private cases referred to the laboratory and they showed evidence of selection. However, graphs have been prepared of these private cases which showed isoimmunization to be used as a check on the results obtained with the public cases. They have been found to bear out the findings so obtained.

In the 2,960 clinic cases examined as a routine, 391 were found to be Rh negative, giving a percentage of 13.2 per cent. For this report we have not broken down those negative patients who showed signs of isoimmunization into categories showing numbers of pregnancies, but have simply recorded the total number found to be immunized. These are 33, or 8.45 per cent, of the Rh-negative cases or 1.12 per cent of the whole.

In each case the diagnosis of erythroblastosis fetalis was confirmed in the child either by autopsy or by blood studies in the children who survived. Also it was proved in all the cases submitted that the children were Rh positive, and in each case where material was available, it was shown that the child's red cells were sensitized and liable to breakdown to a greater or lesser extent by circulating antibody in the mother's serum.

Discussion of Curves

Taken generally the curves show that the later in pregnancy antibodies are demonstrated, taken with a low titer, the better the prognosis, as was expected from previous clinical impressions. Within the compass of the time scale, i.e., up to delivery, the only curves which have tended to show a drop in the later weeks are those in Grade III. This drop has been noted by other observers and its adverse affect on the baby commented on. From our series it was not possible to determine whether the maximum damage to the baby was started at the peak of the curve or during the descent. It has been postulated that the drop in titer of the mother's antibody was an indication of increased absorption of antibody by the fetus. Attractive as this simple hypothesis is, more requires to be known of the protective mechanism, which the fetus has for dealing with a flood of antibodies, as it will be appreciated that a drop in titer from say 1:32 dilution to 1:8 indicates a considerable absolute quantitative drop. This decrease, if it all passed to the fetus in one or two weeks, would surely overwhelm it, and yet some of these babies are born alive in sufficiently good general condition to be salvaged. Every case studied in Grade III did not show this drop, but in these curves it was found as follow up that the drop occurred up to the two to three weeks post partum. Those in Grade IV did not show an appreciable decrease in titer for many weeks post partum. On examining the results for the babies it was found in Grade III that the babies had a better chance of survival if the drop in titer occurred in the postpartum period, which bears out our findings that any shift to the left in any one grade makes the prognosis proportionately worse. One fact emerges and that is the lateness which antibodies are often first demonstrated, as an average, usually about the thirty to thirty-second week. This shows that great care is required in the later weeks to keep a close check on the patient's titer as she comes to term. We regard the appearance of agglutinating antibodies in rising titer as also shadowing the prognosis. When considering the application of the curves to any one case it should be borne in mind that each grade shown is an average curve and deviation from the average should be expected. However it has been found easy to make an accurate forecast by interpolation using the curves and the basic principles outlined; particularly when the patient's history is taken into account. A better baby can be expected if the patient has had no suspicious history in previous pregnancies.

The series given being that of one year's work in the public service of this hospital, is, of necessity, rather limited. Notwithstanding this the results claimed have been amply borne out by checking against the available records for past years and from the private records of our consultant staff who have kindly lent them for this purpose.

One apparent exception to the suggested scheme given above has occurred, and that was in the case of an Rh-negative mother who had previously given birth to an erythroblastotic child. During the pregnancy under review she showed demonstrable blocking antibodies to a titer of 1:4 between the tenth and eighteenth weeks. These then disappeared and she delivered a normal child who was Rh negative. The husband is heterozygous.

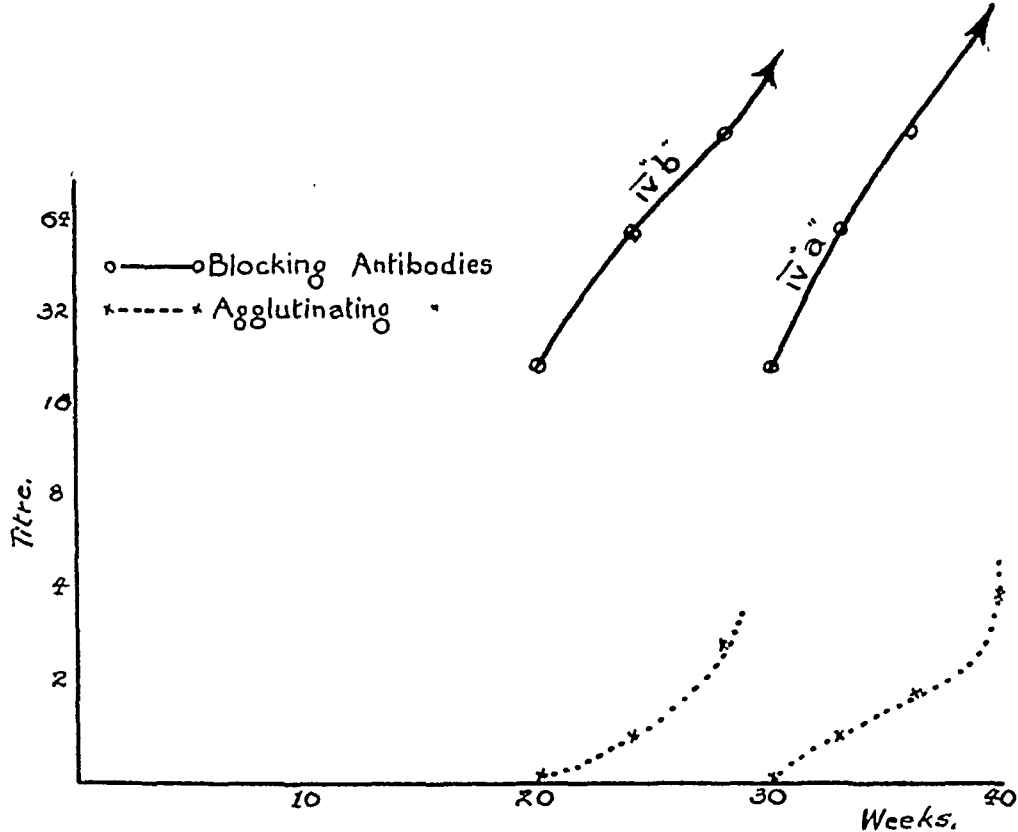


Fig. 4.—Grade IV a; a very sharp rise in the later months to, and above, dilution 1:64 with some agglutinating antibodies. Prognosis very poor for the baby, severe anaemia with oedema. Usually deadborn at term or a week or so before.
Grade IV b; a shift to the left of the first appearance of antibodies in heavy concentration at, or about, the period of theoretical viability. Prognosis. Macerated dead fetus, premature by several weeks.

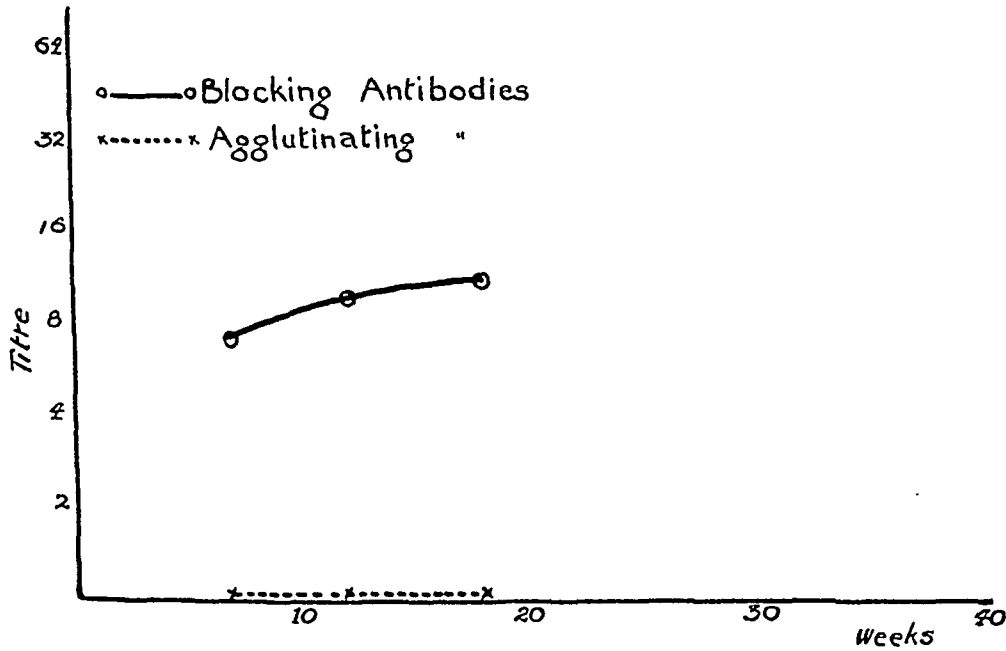


Fig. 5.—Grade V; the appearance of blocking antibodies (with sometimes agglutinating antibodies) in appreciable concentration, dilutions 1:4 and over before the twentieth week. Prognosis hopeless with an Rh-positive baby. Result is abortion or early miscarriage. Future prognosis with a homozygous Rh-positive husband is likely to be uniformly disappointing.

CHARACTERISTICS OF THE NORMAL MENSTRUAL CYCLE*

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A NUMBER of critical studies¹⁻⁴ has shown that the lengths of apparently normal menstrual cycles vary widely, and that absolute regularity in the individual patient is exceptional. The results of some of these investigations are open to re-examination.

The majority of these studies lacks proof of the ovulatory nature of the cycles, i.e., whether true menstruation actually had occurred. In one study⁵ the presence of midperiod pain was taken as the criterion of ovulation; this is suggestive but not conclusive evidence of ovulation or of adequate corpus luteum function. Several studies included many relatively young patients, and in one study all the postmenarchial periods of some patients were included. The data of these studies would include anovulatory cycles.

In none of the studies was any attempt made to eliminate patients with endocrine disturbances save those of sufficient magnitude to be obvious during the routine examinations of student nurses or of women in a contraception clinic. In one study⁶ patients were sent a questionnaire and were followed by mail; the value of these data is questionable.

The existence of uterine factors was determined by pelvic examinations in one study.⁷ No mention of routine pelvic examination is made in a study of student nurses.³

There are, finally, lesser factors which are known to influence the regularity of menstrual cycles, as minor illnesses, changes in environment, travel, or alterations of working hours (especially applicable to nurses). Although gross disturbance in function may have been eliminated in the selection of the final data,³ there is no record that these supposedly minor factors were discounted.

The data of these studies provide interesting comparisons. Two of the curves of Fig. 1 are quite similar, but differ widely from the other three which show less variation in the cycle length. Both these curves were obtained from studies of student nurses, whereas the other three were based on heterogeneous groups.

Materials and Methods

Menstrual data collected in the Endocrine Division avoid many of the drawbacks of data previously reported by others; they appear to be ideally suited for the establishment of the true norms of menstruation.

During the course of routine sterility surveys⁸ both members of the couple are studied intensively. The survey of the wife includes a complete and thorough

*Part of the expenses of these studies was defrayed by grants to one of us (E. C. H.) from the National Committee on Maternal Health, Duke University Research Council and Ayerst, McKenna and Harrison, Ltd.

Practical Use of the Curves

The usefulness of being able to give a prognosis for the fetus along general lines is apparent. In some cases it may be considered advisable to terminate the pregnancy a few weeks before term by cesarean section with a view to saving the fetus from excessive breakdown of its cells. A study of the curves shows that in cases which fall into Grades I and II this may be justified. However when the titration curves approximate to Grade IIIb and IV, then it is questionable whether the increased risk to the mother is justified when the prognosis to the baby, even when a well-organized resuscitation team is at hand, is so poor.

It is felt that, for those patients who come under Grades IV and V, if the husband is homozygous positive, then further pregnancies should not be attempted.

In our cases in which antibodies are demonstrated during the antenatal period preparations are made as the woman is brought to hospital for delivery, to have a resuscitation team ready to take charge of the infant. This team, which consists of a "Transfusion Officer" and a Pediatrician, has at their disposal Rh-negative blood, cross matched against the mother and laboratory facilities on a 24-hour basis quickly to determine, from heparinized cord blood the infant's Hb, packed cell volume, icteric index, and the Rh of the blood, together with any evidence of sensitivity of the infant's red cells. On these findings the appropriate treatment for the infant is based.

Protection of the Fetal Liver

On the advice of one of us (N. W. P.) late in this series an effort was made to protect the fetal liver from excessive damage in cases of known isoimmunized pregnant women. The method used was to have the mother take adequate doses of Methionine by mouth from the time when antibodies were first demonstrated until she was delivered. The infant is also given Methionine by mouth during the immediate postnatal period. In a small series of six cases the results have been encouraging. Further work is proceeding and will be the subject of a further communication.

Summary

A graphic method for estimating the prognosis of the child in cases of isoimmunization against the Rh factor during the antenatal period is given.

The technical details are outlined.

Suggested uses for this method of prognosis are offered.

The taking of methionine by the mother is put forward as a method of protecting the fetal liver.

This work was made possible in part by a grant from the Baxter Laboratories, Inc., and also the brand of Methionine used in this investigation was Meonine manufactured by John Wyeth & Brother (Canada) Limited, Walkerville, Ont.

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history and physical examination (with an emphasis on the gynecologic and endocrine aspects), basal metabolism tests, roentgen-ray examination of the sella turcica, routine urine and blood examinations, special blood chemistry studies when indicated, tubal tests with radiopaque oil, postcoital tests, endometrial biopsies at the onset of bleeding, and basal (rectal) temperature records. The importance of timing these studies with the menstrual cycle necessitates close and constant supervision of the patients for four to six months or longer.

For this study, 109 patients were selected. No more than 13 cycles of any patient were used: accordingly, no one patient contributed more than 2.5 per cent of the data. No patient with organic or functional ovarian disorders, endocrine disease, or with uterine factor as determined by history, pelvic examination, or uterosalpingography was included. No patient was less than 20 years of age. Six patients (5.5 per cent) were 20 to 24 years old, 34 (31.2 per cent) 25 to 29 years old, 43 (39.5 per cent) 30 to 34 years old, 22 (20.1 per cent) 35 to 39 years old, and 4 (3.6 per cent) were 40 to 42 years old. A total of 524 cycles of these 109 patients followed with basal temperature records, was studied. On these records, minor events as late hours, restless sleep, or travel were marked; febrile illnesses, of course, were immediately apparent; these records were excluded from our studies. The presence of intermenstrual spotting, or the omission of temperature recording for more than two to three days also eliminated some records from study.

Arbitrary criteria were established so that the basal temperature records could be analyzed in a uniform fashion. The *time of ovulation* was calculated from the last temperature before the beginning of the continuous (progestational) rise. The *average temperature rise* was estimated from the difference of the mean preovulatory and postovulatory temperatures. The *duration of temperature rise* was measured from the beginning of the progestational rise to the end of the phase of constant rise. Cycles in which no definite time of ovulation could be established from the basal temperature record, and which were nevertheless not definitely anovulatory, were termed *indeterminate cycles* and were treated as a separate group. The *duration of bleeding* included all days during which there was any show of menstrual blood. The criteria for estimating the presence and degree of progestational response in endometrial biopsy specimens (taken within eighteen hours after the onset of bleeding) were ones employed for many years on our service.

Results

Of the 524 recorded cycles 500, or 95.4 per cent, were ovulatory, 13, or 2.5 per cent, were anovulatory, and 11, or 2.1 per cent, were indeterminate, as judged by basal temperature records. All 58 biopsies from cycles with ovulatory rises revealed progestational endometriums, thus confirming the interpretation of the temperature curve.

Length of the Menstrual Cycle.—The length of the 500 menstrual (i.e., ovulatory) cycles is plotted as curve 5 in Fig. 1. No cycles shorter than 19 days were recorded. Only one cycle longer than 60 days was observed. Only 3.2 per cent of the cycles was 19 to 22 days in length, 21.4 per cent was 23 to 25 days in length, 53.6 per cent was 26 to 29 days in length, 17.8 per cent was 30 to 36 days in length, and 4 per cent was longer than this. Thus, over half of the normal menstrual cycles was 26 to 29 days in length, and 92.8 per cent fell within the 23 to 36 days interval.

Comparison of our curve with those of other workers reveals several interesting features. When anovulatory cycles are eliminated, the short ones (less than 19 days) apparently disappear from the curve. All the curves show an approximately equal and rather low incidence of cycles longer than 36 days.

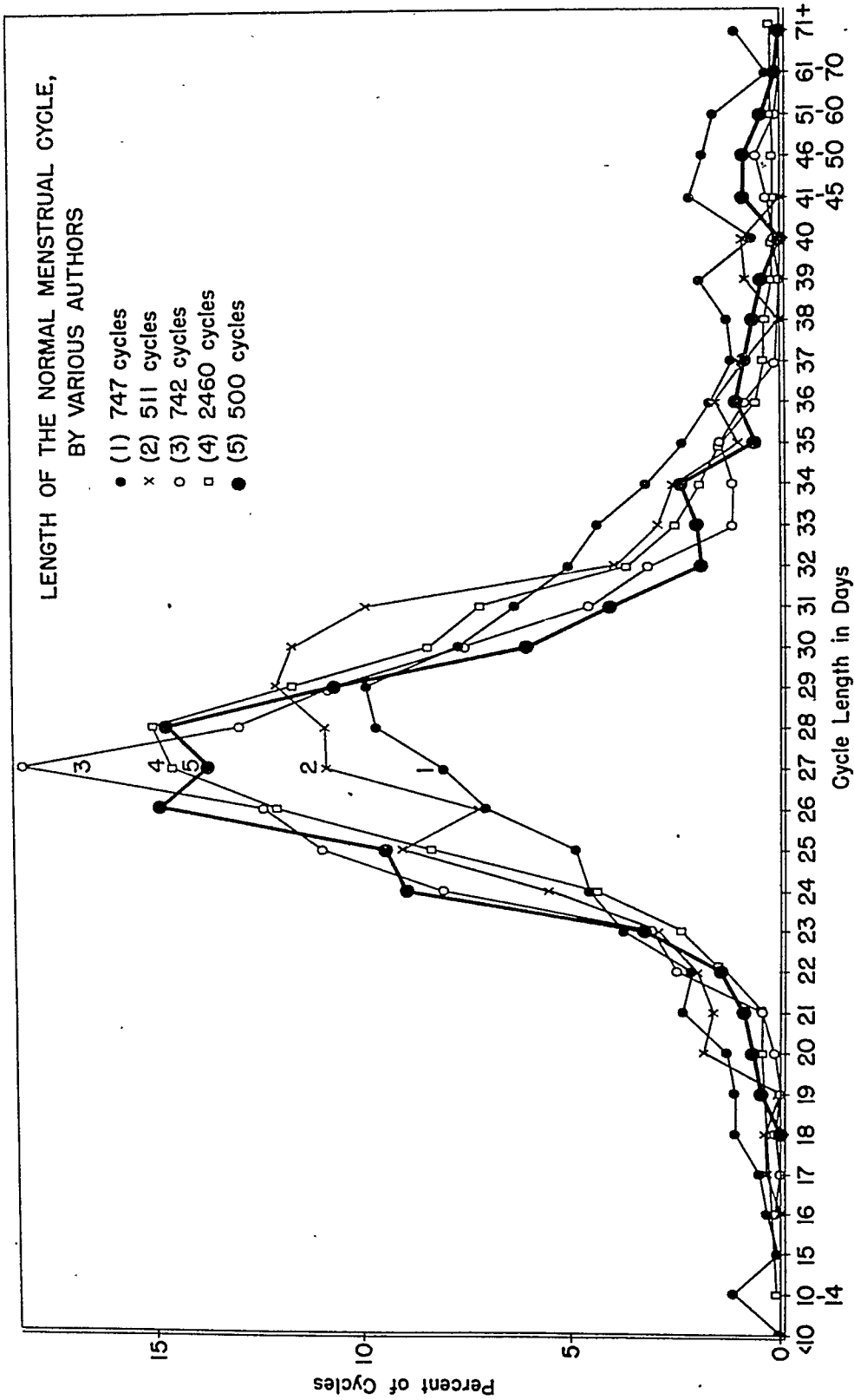


Fig. 1.—Graphic representation of the length of the normal menstrual cycle reported by various authors.

The Estrogenic Phase.—Fig. 2 shows the length of the estrogenic phase as measured in 495 ovulatory cycles. In the majority of women (79.6 per cent) this phase was 10 to 16 days in length. A small number (1.9 per cent) was less than 10 days in length, but a significant proportion was relatively long. The estrogenic phase was 17 to 25 days long in 15.6 per cent, and longer than 25 days in 2.9 per cent.

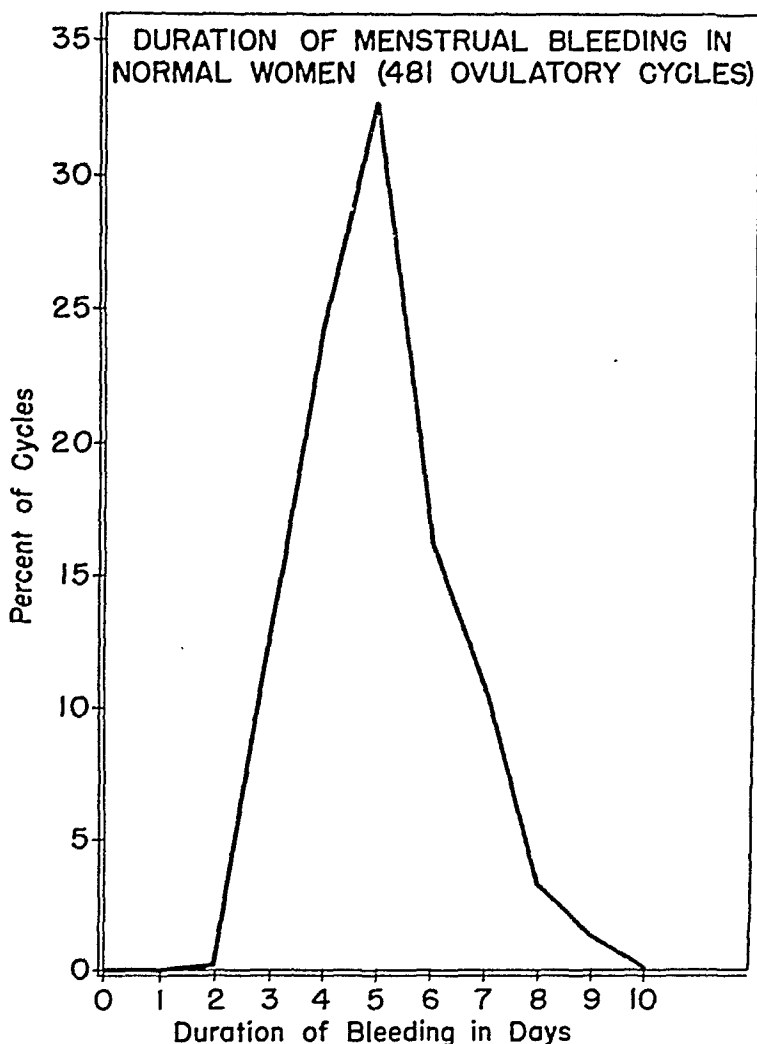


Fig. 3.—Graphic representation of the duration of bleeding in 481 ovulatory cycles in normal women.

The Progestational Phase.—Fig. 2 also shows the length of the progestational phase of 490 cycles. One progestational rise was only 5 days long. Otherwise, there was none shorter than 8 days or longer than 19 days. It is believed usually that the progestational phase is fairly constant, ranging from 11 to 14 days in length. In our material only 69.5 per cent of the cycles showed this duration. The progestational phase was 10 to 16 days in length in 94.0 per cent, less than 10 days in 1.8 per cent, and 17 to 19 days in length in 4.3 per cent.

These data agree with the belief that the unusual length of the ovulatory cycles results from a prolongation of the estrogenic phase. In nearly one-fifth of the cycles this phase was longer than 17 days. It is also interesting that a short estrogenic phase is unusual. The measurements of the progestational phase, however, do not confirm its supposed constancy; approximately two-thirds of

There is no reason to believe, accordingly, that any significant percentage of the long cycles observed by others was anovulatory. Curves 1 and 2, which differ most, are based on a selected group (nursing staff) which is often under unusual environmental strains. It is also interesting to note that the figures of Haman⁷ based on 2,450 cycles in mature women, attempting the "safe period" type of contraception, agree most closely with the frequency distribution observed in our patients. This may be explained by the greater maturity of his

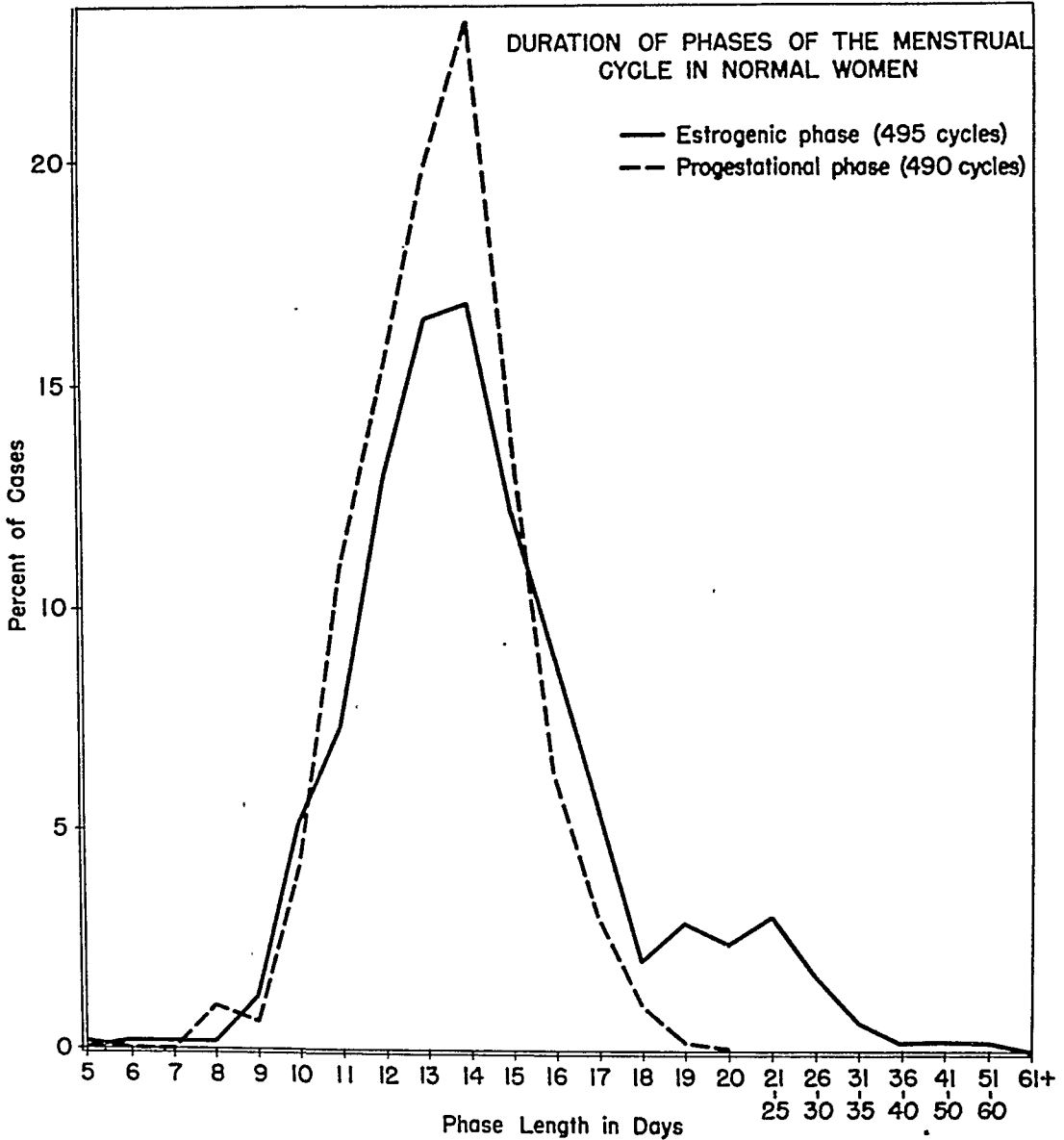


Fig. 2.—Graphic representation of the length of the phases of the menstrual cycle in normal women.

patients (with a lower incidence of anovulatory cycles), by the variety of environmental status, and by the sheer weight of numbers, which would tend to dilute out the minor factors.

The anovulatory cycles ranged from 16 to 38 days in length. Their relatively small number (a total of 13 cycles) makes any plotting of the frequency distribution valueless. There were 11 indeterminate cycles. These ranged from 15 to 37 days in length, and were also widely scattered across this range.

No mention has been made of the actual amount of bleeding. Although this was recorded for most women, it was felt that the pad count and the patient's own estimate of the degree of pad saturation were far too individual to yield information of any real value. We have made, therefore, no attempt to draw conclusions from these data.

Basal Temperature Records.—The difference in the mean temperatures of the pre- and postovulatory phases was estimated in 486 cycles. In a small number (11.3 per cent) this difference was relatively small (0.2 to 0.5° F.). The rise usually was 0.6 to 0.9° F. (78.9 per cent). In 9.8 per cent of the cycles the temperature rise was 1° F. or more. The greatest rise observed was 2.0° F. in two cycles of the same patient (0.4 per cent). This range emphasizes the value of recording the temperatures in degrees Fahrenheit and on a relatively large scale, as shown in the sample chart (Fig. 4). The use of a smaller scale or of degrees Centigrade makes the recognition of a significant number (11.3 per cent) of ovulatory cycles very difficult. It is possible also that a greater variability in oral temperatures may conceal a considerable proportion of truly ovulatory cycles.

The duration of the postovulatory rise is of interest. This was estimated with reasonable accuracy in 459 cycles. In 13.7 per cent the temperature rose sharply and leveled after one day. In 69.3 per cent the rise continued sharply for one to four days, and then leveled. In the remaining 30.7 per cent the rise was more constant and gradual, extending over a period of five to nine days. In a small number of cycles,¹¹ not included in these figures, there were signs of a very gradual, lowgrade temperature rise, neither conclusively ovulatory in character nor definitely anovulatory. Unfortunately, no bleeding biopsies at the end of these 11 cycles were available. These were "indeterminate" cycles and they have been excluded from the statistical calculations.

At the present time we have no idea of the significance of the slope of the progestational rise. Whether this reflects the degree of corpus luteum activity, whether it is purely an individual response, or perhaps a combination of these and other factors is a matter of conjecture. Our studies do not yield new information of the exact correlation of ovulation and the basal temperature rise. It is known that a characteristic temperature rise may be produced in the castrate by the injection of progesterone.⁹ We have accepted this rise, therefore, as presumptive evidence of ovulation. Whether the observed temperature rise is entirely a progesterone reaction phenomenon, whether the actual process of ovulation plays a role, and how soon after actual ovulation the basal temperature is affected are not known. Therefore, our estimates of the time of ovulation are probably later (it may be by as much as two to three days in some cycles) than the actual ovulation.

Correlation of Endometrial Biopsies and Basal Temperature Records.—A total of 61 bleeding biopsies following a recorded cycle was available for study; 58 of these were from ovulatory cycles, and 3 were from anovulatory cycles, as judged by basal temperature records. *All 58 biopsies after ovulation temperature curves showed histologic evidence of progestational change.* In 86.3 per cent (50 biopsies) histologic and temperature length of the progestational phase agreed within forty-eight hours. In two instances (3.5 per cent) histologic change was less advanced than the duration of the progestational temperature elevation indicated (i.e., there was more than two days' difference in the readings). In six cycles (10.2 per cent) the progestational change was advanced further than was expected from the duration of the temperature elevation. In these eight cycles the curves did not show any unusually high or low temperature rise. It is not clear, therefore, whether this discrepancy is due to error in our method of estimation or whether it may possibly indicate quantitative differences in corpus luteum activity which are not shown by the basal

the cycles fell within the 11 to 14 days' range. It required a 7-day interval (10 to 16 days) to include most of the cycles. Both very short and very long phases, however, were rare. The progestational phase is more constant in length than the estrogenic phase.

Duration of Bleeding.—Data on the duration of bleeding were available in 481 cycles. The frequency distribution is shown in Fig. 3. In one cycle (0.2 per cent) bleeding was less than 3 days in length and in none was it longer than 9 days. In 95.4 per cent of patients, bleeding was 3 to 7 days in length; however, in more than two-thirds (68.4 per cent) of all the cycles, bleeding was 3 to 5 days in duration.

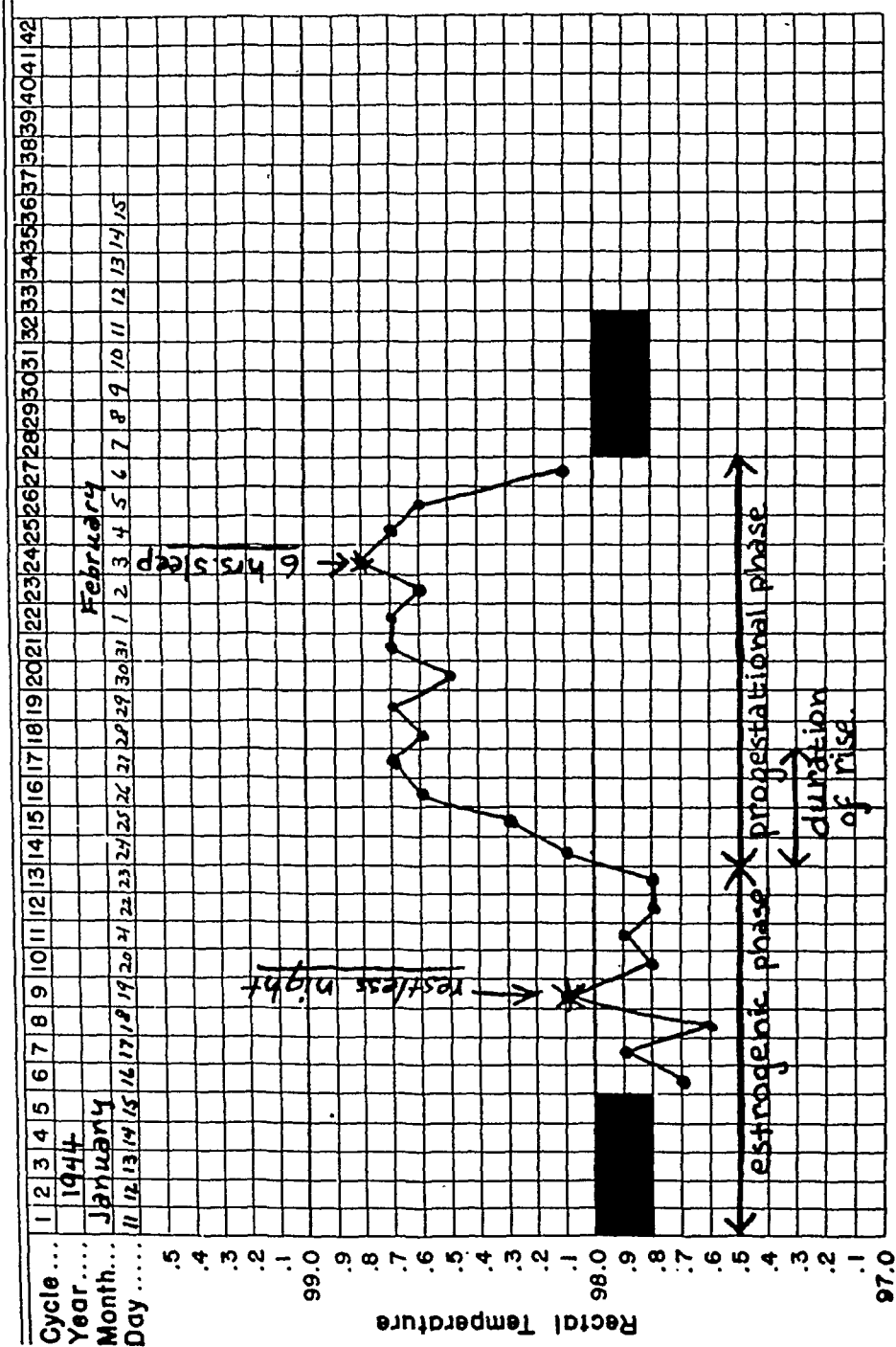


Fig. 4.—Typical basal temperature chart, showing the method of recording and evaluating the data.

RELATIONSHIP BETWEEN CERVICAL MUCUS AND BASAL TEMPERATURE CYCLES*

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CYCLIC variations in some of the physical properties of cervical mucus of normal women are well recognized. The amount of mucus is greatly increased during the ovulatory phase of the menstrual cycle, and at this same time a marked decrease in the viscosity and in the cellularity of the mucus is noted.¹⁻⁷ Spermatozoa can penetrate the mucus to an appreciable distance only during this period of the cycle and during menstruation.^{1-4, 7, 8} These changes in the cervical mucus have been shown to be under hormonal influence^{4, 9-11} and coincide with the time of ovulation.

Another method for estimating the approximate time of ovulation is based on the fact that at this time the basal temperature shifts from a lower to a higher level. Reviews of the literature on this subject are given by Barton,¹² Pommerenke,¹³ and Tompkins.¹⁴

Barton and Wiesner¹⁵ observed in their studies of fertile women that the cervical mucus cycle bears a definite time relationship to the basal temperature cycle. According to these workers the mucus increases in amount and becomes transparent and acellular just before the temperature shift. After one to three days it decreases in quantity and again becomes cellular. In previous communications the present authors also showed that the temperature shift occurs during the time of increased mucus production in midcycle.^{5, 7} These results were based on a relatively small series of cycles on relatively few subjects. Many additional observations on a larger group of subjects have now confirmed this finding and have also made possible a better understanding of the time relationship between these two phenomena.

Methods

A total of 15 healthy young women who had normal menstrual histories and normal pelvic structures served as subjects in this study. Eight of these women are of known fertility, two of them having become pregnant during cycles under observation. Most of these subjects were followed through at least three or four cycles, and four of them were studied for from eight to fifteen cycles. Daily observations, save during menstruation, were made whenever possible. The cervical mucus was obtained from the external os and from the cervical canal by aspiration, using the method previously reported.^{5, 7} An effort was made to obtain all the mucus available at any one time, and all specimens were weighed. Basal temperature, taken vaginally, were recorded in the usual manner.

*Aided by a grant from the Ortho Research Foundation, Raritan, N. J.

temperature record. From the point of view of fertility, only two biopsies yielded information significantly different from that obtained from the temperature records; this satisfactory correlation may eliminate the necessity of performing endometrial biopsies in many patients.

Three biopsies were obtained after cycles judged anovulatory from the temperature record. Two of these showed late estrogenic endometria, compatible with the length of the cycle. The third biopsy showed full-blown progestational changes despite a flat temperature curve. If this temperature record is accurate, and we have no reason to doubt it, no explanation for the discrepancy is apparent.

Summary and Conclusions

For many years the paradoxical statement of Fraenkel that "the only regular feature of menstruation is its irregularity" has been repeated in the literature. These statistics indicate that most features of truly normal menstruation are fairly constant and do not vary more widely than other physiologic functions. There is no doubt that menstruation, as the final common manifestation of highly complex neural and hormonal influences, is a delicate indicator of disturbances in these fields. This, however, does not justify the statement that true (ovulatory) menstruation is an unpredictable, erratic phenomenon.

The menstrual cycles of 109 carefully investigated, healthy adult women were studied by means of basal temperature records and endometrial biopsies at the onset of bleeding. A total of 524 cycles, presumably free of the influence of unusual stresses, forms the basis of this report. These cycles were analyzed statistically for cycle length, duration of the estrogenic and progestational phases, duration of menstrual bleeding, characteristics of the basal temperature rise, and correlation of temperature curve and endometrial biopsy.

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any particular individual, because in other cycles the same subjects had temperature curves with clearly defined shifts. Since the basal temperature is influenced by numerous external factors,¹²⁻¹⁴ it is not surprising that the temperature curves are subject to some variation. Although the curves were definitely diphasic in an additional eight cycles, the records were incomplete in the ovulatory phase, making it impossible to determine the exact time of the shift.

The temperature shift occurred later in the longer cycles, and corresponded in this respect with the information obtained from the mucus production studies. The shift occurred from twelve to sixteen days after the onset of the last menses in only 53 per cent of the cycles, the lengths of which varied from twenty-two to thirty-seven days. However, when the days of the cycles were numbered in reverse, as already explained, the temperature shift occurred from sixteen to twelve days ($14 \text{ days} \pm 2$) before the subsequent menstrual period in 88 per cent of the cycles.

Sufficient information was available to correlate the time of the temperature shift with the period of increased mucus production in a total of 57 cycles in 14 subjects. In 38 of these cycles the temperature shift was clearly defined, and in only two instances did the shift occur at a time when the mucus was not increased in amount. In one of these cases the shift occurred two to three days before the period of increased mucus secretion began, and in the second instance the temperature shift occurred two to three days after the period of increased mucus production had ended.

In 27 of the 57 cycles it was possible to correlate the temperature shift with the day of maximal secretion. In 14 of these cycles the maximal secretion occurred at the time of the temperature shift; in five cycles the maximal secretion occurred one to two days before the shift; and in eight cycles the maximal secretion occurred one to two days later. In the latter two groups, even though the mucus secretion was not at the peak of production, it was markedly increased at the time of the shift.

The exact time of the temperature shift was obscured in 19 cycles by day to day fluctuations even though the entire curves were diphasic in character. However, the increased quantity and the accellular appearance of the cervical mucus that was observed during the period in question suggested that the temperature shift must have occurred at this time.

Discussion

The time when the human female is susceptible to fertilization is probably limited to a very few days in the menstrual cycle; well defined periods of sterility and fertility support this conclusion. While individual variations are admitted, the bulk of evidence, both direct and indirect, places the ovulatory phase when fertilization may occur at about 14 days prior to the next menstrual period.

Basal temperature variations were correlated with phases of the menstrual cycle as early as 1904 by Van de Velde.¹⁷ This shift in temperature from a lower to a higher level, occurring as it does about fourteen days prior to the succeeding menstrual period, has come to be regarded as intimately associated with the ovulatory process.¹²⁻¹⁴ Furthermore, it has become a not uncommon clinical practice to instruct women who are planning pregnancies to be especially mindful of the time of the month when the rise in temperature occurs. In this phase of the cycle the entire generative tract undergoes changes adapting it to the fertilization and gestation processes. Among these

Results

A total of 80 cycles have been observed, and in all of these an increased mucus production was noted at midcycle. As has been reported,^{5, 7} the amount of mucus which can be obtained from the canal at a single aspiration is small, ranging from 15 to 50 milligrams, in the pre- and postovulatory phases of the cycle. As the cycle enters the ovulatory phase, the amount of mucus secreted increases markedly and reaches a peak production approximately in the middle of the ovulatory phase. The amount of mucus which can be aspirated at the time of this maximal secretion varies from 113 to 738 milligrams, with an average of 268 milligrams. The quantity then falls to the postovulatory level of 15 to 50 milligrams in two to three days. The individual specimens of mucus were assigned to the different phases of the cycle on the basis of the general knowledge of the cycle as a whole, the amount aspirated, and the degree of cellularity of the sample.

On the basis of quantity and degree of opalescence of the mucus secretion, it was possible to determine the length of the ovulatory phase within one day in 37 cycles. These observations were made on a group of 12 subjects whose menstrual cycles ranged from 22 to 37 days in length. The period of markedly increased mucus production varied from three to seven days, with an average of five days (Table I). It was noted that in 12 cycles of thirty days or more the duration of the increased mucus secretion was never less than five days. The time in the cycle at which this phase of increased mucus secretion appeared was related more closely to the time of the onset of the subsequent menses than to the time of the preceding menstrual period as shown by the fact that the period of increased mucus secretion occurred later in the cycles of longer length (Table II).

The day on which the cervical secretion attained its maximal production was noted in 53 cycles ranging in length from twenty-two to thirty-seven days (Table III). These observations were made on 13 subjects. When the days of the cycle were numbered in the usual manner, i.e., by counting the first day of the preceding menstrual flow as day one, the time of maximal mucus secretion varied from day 9 to day 24. In only some 50 per cent of these cases did the day of maximal secretion occur between days twelve and sixteen after the last menses. This low percentage can be explained by the fact that there is considerable variation in the lengths of the cycles observed. However, when the days of these same cycles were numbered in reverse, i.e., as days before the onset of the subsequent menses, it was found that the maximal secretion occurred over a much shorter range, namely eighteen to eleven days, regardless of the length of the cycle. In 83 per cent of the cycles the variation was only from sixteen to twelve days before the onset of the next menstrual period. This is further evidence that the length of the phase between ovulation and the succeeding menses is more or less fixed at $14 \text{ days} \pm 2$,¹⁶ while the length of the preovulatory phase varies with the length of the cycle.

Although the day of maximal secretion varied from 18 to 11 days before the subsequent menses for the entire group, when the cycles of a particular individual were considered separately the range was much less (Table IV). This may be explained by postulating that some individuals consistently appear to have a longer postovulatory phase than others.

Basal temperatures were recorded in a total of 65 cycles on 14 subjects, and all of these showed curves of the diphasic type characteristic of normal women in the reproductive age. In 43 of these cycles the time of the temperature shift from a lower to a higher level was sharply defined. In 14 cycles these transitions were not distinct, although the over-all appearance of the curves were of the diphasic type. These indistinct curves were not limited to

TABLE IV. INDIVIDUAL VARIATIONS IN TIME OF OCCURRENCE OF MAXIMAL MUCUS SECRETION

| SUBJECT | NUMBER OF CYCLES OBSERVED | LENGTH OF CYCLES OBSERVED (DAYS) | RANGE OF DAYS ON WHICH MAXIMAL SECRETION OCCURS (DAYS BEFORE SUB- SEQUENT MENSES) |
|---------|------------------------------|--|---|
| 6 | 10 | 29-37 | 15-13 |
| 5 | 8 | 22-30 | 14-11 |
| 7 | 8 | 27-31 | 17-12* |
| 1 | 4 | 25-27 | 18-16 |
| 9 | 4 | 25-29 | 17-14 |
| 13 | 3 | 24-27 | 16-13 |
| 11 | 3 | 24-27 | 14-12 |
| 8 | 3 | 25-30 | 13-11 |
| 2 | 3 | 26-27 | 16-13 |
| 3 | 2 | 26-27 | 17-15 |
| 12 | 2 | 28-30 | 16-15 |
| 16 | 2 | 34-36 | 17-15 |

*If the two cycles in which maximal mucus secretion occurred on day seventeen and day twelve, respectively are omitted, maximal secretion occurred on day thirteen or fourteen in the remaining six cycles.

the time of the basal temperature shift is additional evidence that the exact sequence of events associated with human ovulation are not yet clearly understood. At the present time the only definite conclusion that can be drawn is that in normal women, only rarely does the temperature shift occur when the cervical mucus is not increased.

In planning pregnancy in women of low fertility and in employing artificial insemination it is highly desirable to know when and under what conditions successful insemination is most likely to occur. A study of the cervical mucus cycle together with the basal temperature cycle should furnish valuable information relative to the period of maximal fertility.

Summary

The length of the ovulatory phase in the normal menstrual cycle was determined on the basis of the increased quantity and decreased cellularity of the cervical mucus secreted at this time. This phase of increased secretion was found to vary from three to seven days in length and occurred later in cycles of longer length. The shift in basal temperature was also observed and it was found to occur, with rare exceptions, only during this phase of increased mucus secretion. The day of maximal mucus production usually occurred from sixteen to twelve days before the onset of the subsequent menstrual period regardless of the length of the cycle. When the day of maximal mucus secretion was correlated with the time of the basal temperature shift, it was found that the two phenomena occurred simultaneously in only 52 per cent of the cycles studied. In 18 per cent of the cycles the maximal secretion occurred one to two days prior to the shift, and in 30 per cent of the cycles it occurred one to two days later. A study of the cervical mucus cycle together with the basal temperature cycle has been suggested as a possible aid in planning pregnancies.

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TABLE I. DURATION OF OVULATORY PHASE AS DETERMINED BY INCREASED MUCUS SECRETION

| NUMBER OF DAYS DURATION | NUMBER OF CYCLES OBSERVED |
|----------------------------|------------------------------|
| 3 | 4 |
| 4 | 7 |
| 5 | 11 |
| 6 | 9 |
| 7 | 6 |

TABLE II. TIME IN CYCLE AT WHICH PERIOD OF INCREASED MUCUS SECRETION OCCURS

| NUMBER OF CYCLES OBSERVED | LENGTH OF CYCLES OBSERVED (DAYS) | RANGE OF PERIOD OF INCREASED MUCUS (DAYS)* |
|------------------------------|--|--|
| 1 | 22 | 9-14 |
| 1 | 24 | 9-12 |
| 6 | 25 | 8-17 |
| 2 | 26 | 10-14 |
| 6 | 27 | 10-21 |
| 3 | 28 | 11-21 |
| 6 | 29 | 11-19 |
| 3 | 30 | 13-21 |
| 2 | 31 | 15-21 |
| 2 | 33 | 17-23 |
| 2 | 34 | 15-21 |
| 1 | 35 | 20-24 |
| 2 | 36 | 17-25 |

*The first day of flow in the preceding menstrual period is counted as day one of the cycle.

TABLE III. TIME IN CYCLE AT WHICH MAXIMAL SECRETION OCCURS

| NUMBER OF CYCLES OBSERVED | LENGTH OF CYCLES OBSERVED (DAYS) | RANGE OF DAYS ON WHICH MAXIMAL SECRETION OCCURS | |
|------------------------------|--|--|----------------------------------|
| | | DAYS SINCE PRECEDING MENSES | DAYS BEFORE SUBSEQUENT MENSES |
| 1 | 22 | 11-12 | 11-12 |
| 1 | 23 | 12 | 12 |
| 3 | 24 | 11-13 | 12-14 |
| 6 | 25 | 9-14 | 12-17 |
| 6 | 26 | 10-15 | 12-17 |
| 9 | 27 | 10-15 | 13-18 |
| 4 | 28 | 13-18 | 11-16 |
| 8 | 29 | 13-18 | 12-17 |
| 5 | 30 | 15-19 | 12-16 |
| 3 | 31 | 17-18 | 14-15 |
| 1 | 33 | 20-21 | 13-14 |
| 2 | 34 | 18-19 | 16-17 |
| 1 | 35 | 22 | 14 |
| 2 | 36 | 21-23 | 14-16 |
| 1 | 37 | 23-24 | 14-15 |

changes is the elaboration of a copious cervical secretion of low viscosity and low cell content. Since in vitro tests demonstrate that the cervical mucus secreted in the ovulatory phase is most readily penetrable by spermatozoa, one may be permitted to surmise that a like condition exists in vivo.

The present study indicates that a close correlation exists between the phase of increased cervical secretion and the time of the shift in basal temperature. Both phenomena seem to be under hormonal control, but the fact that the maximal secretion of cervical mucus does not necessarily coincide with

POSTPARTUM HEADACHE AFTER LOW SPINAL ANESTHESIA IN VAGINAL DELIVERY AND ITS TREATMENT

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THE increasing use of spinal anesthesia in obstetrics prompted us to issue a preliminary report in the hope that those cases of headache commonly attributed to the anesthetic may be alleviated by the suggestions to be offered.

Headache following the use of low spinal or saddle block anesthesia for vaginal delivery is an annoying though transitory complication in some cases. The incidence of postlaparotomy spinal headache in cesarean section and various gynecologic operations was found by us to be much lower than in vaginal delivery. In the latter, a headache incidence of 15 per cent was noted in a series of 300 cases. As we were unwilling to forego the many advantages of spinal anesthesia in obstetrics, as set forth in an earlier publication,¹ the mechanism and treatment of the postpartum spinal headache became a practical problem, particularly since it was the only postpartum complaint attributable to the anesthetic. The higher headache incidence in vaginal, as compared with abdominal deliveries, indicated that there were certain factors concerned in its production which do not usually operate in cases subjected to cesarean section or other abdominal operations under spinal anesthesia.

An unusual case of severe and persistent postpartum headache following the subarachnoid administration of 50 mg. of procaine hydrochloride for vaginal delivery first focussed our interest on the necessity for study of this problem.

M. G., primipara, 21 years old, was delivered easily on Aug. 17, 1945, by low forceps of a living female. At 8 cm. dilatation, 50 mg. of procaine were injected slowly into the fourth lumbar interspace. Anesthesia was effective; prompt, spontaneous effacement and full dilatation of the cervix quickly followed; and delivery was uneventful. On the third postpartum day, a mild frontal and occipital headache set in, and grew progressively more severe. Full therapeutic doses of codeine, aspirin, caffeine, benzedrine, ephedrine, gynergen, and ammonium chloride, given at various times, were ineffective throughout her hospital stay of ten days. The puerperium otherwise was normal. On the ninth postpartum day, when she was discharged from the hospital, her headache was unrelieved. On the twelfth postpartum day, pounding in the ears and persistence of headache necessitated continuous confinement to bed at home. Lying flat afforded no relief, and sitting in bed intensified the headache and caused throbbing of an unbearable degree. Examination by one of us (W. A.) on this day disclosed no pelvic or other physical abnormality. Blood pressure in bed was 110/70, and pulse rate 80. On standing upright out of bed she experienced an accession of headache and throbbing in the ears, the pulse rate rose to 130 per minute, and the blood pressure fell to 60/0. This evidence of orthostatic hypotension and tachycardia suggested the application of firm, manual, abdominal compression. Amazing and instantaneous relief of symptoms followed.

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relieved, while if it be of other origin, it will remain unaffected. If orthostatic hypotension and/or tachycardia are found, the headache is most likely of spinal anesthesia origin. Headaches of other origin were excluded from this study. There is a strong element of suggestion in the development of any postpartum headache, and we have learned from experience that it is wiser not to question for its onset too overtly, but rather by indirection, or to wait until the patient volunteers the complaint. A discreet nurse helps considerably, while injudicious questioning by attendants causes a higher incidence of this complaint.

Discussion

The two factors which we consider responsible in most cases of spinal headache in obstetrics are: first, and more important, the sudden release of intra-abdominal pressure following delivery of the child, superimposed on the action of the anesthetic; and second, spinal fluid leakage. The latter factor can be minimized by the use of a fine gauge needle (No. 22) which permits the fluid to escape slowly in drops.² Rapid release of spinal fluid in a stream, such as occurs under increased pressure or with a wide-bore needle (No. 18), is more likely to be followed by headache.

Spinal anesthesia headache is usually attributed to traction by the brain on various pain sensitive structures which anchor it to the cranium. Such traction follows a disturbance in intracranial hydrodynamics initiated by leakage of spinal fluid at the puncture site.³ Some observers have recently questioned the leakage theory.⁴ Nevertheless, our own observations indicate that leakage does play a part in the initiation of the headache. That this is so is evidenced by the fact that the headache usually begins on the third or fourth postpartum day, by which time sufficient fluid has leaked through the defect in the dura to allow the brain to settle down and rest on the cranial bed. Furthermore, when a simple diagnostic tap is performed without reintroduction of spinal fluid, headache usually appears within twelve hours. Were leakage not a factor, this differential in time of onset of the headache would be difficult to explain.

The more important factor in the initiation of the headache after spinal anesthesia we believe to be the pooling of blood in the splanchnic vessels induced by the sudden release of intra-abdominal pressure occurring post partum, which is further augmented by the vasomotor paralysis due to the action of the spinal anesthetic on the sympathetic nerves. Though this was not evidenced clinically in all cases by the presence of orthostatic hypotension and/or tachycardia, the relief afforded by abdominal compression in both groups indicated that their ability to make the necessary compensatory vascular adjustments was faulty. The majority of patients (85 per cent) do not develop postspinal anesthesia headache because of a compensatory vascular competence, or minimum spinal fluid leakage, or both.

In several instances it has been possible to predict the onset of spinal headache by observing susceptibility to orthostatic hypotension and tachycardia. The headache is more often observed in the puerpera with a flabby, thin abdominal wall, often with preceding overdistention during pregnancy. In a typical case of spinal postpartum headache firm manual compression of the

Release of abdominal compression was succeeded by prompt recurrence of headache and throbbing. A very tight abdominal binder was forthwith applied to maintain constant compression, and the patient was enabled at once to resume her usual duties unhampered by return of symptoms. This dramatic therapeutic result in the case of an unusually severe postlumbar puncture headache encouraged further investigation of its *modus operandi*, and the following routine was instituted.

Procedure

Three hundred patients delivered vaginally under spinal anesthesia were questioned daily during the postpartum period for the occurrence of headache. As soon as any complaint was registered, the following observations were made:

1. Blood pressure reading and pulse rate lying in bed.
2. Blood pressure readings and pulse rates, one minute and three minutes respectively, after standing out of bed.
3. Effect of firm, abdominal compression on headache, blood pressure, and pulse rate in and out of bed.

As a control, similar observations were made on a group of puerperae in whom no headache had developed by the fifth postpartum day.

Results

Of the 300 patients examined, headache occurred in 45. It was noted that postspinal anesthetic headache in this group most often appeared on the third or fourth postpartum day. Twenty-three of the patients developing headache after spinal anesthesia (slightly over 50 per cent) exhibited orthostatic hypotension of varying degree which was in almost every instance associated with orthostatic tachycardia. No direct relationship was demonstrable between the degree of orthostatic hypotension and/or tachycardia and the intensity of headache. Individual emotional reaction and varying threshold for pain, in addition to certain unknown factors, are probably accountable for this finding. Abdominal compression, at first tentatively by hand to test immediate response, and then, by means of a tight binder resulted in a complete, or almost complete, relief of postlumbar puncture headache in most cases (90 per cent). A many-tailed, abdominal binder, extending from the symphysis pubis to the xyphoid process, reinforced by folded towels inserted between binder and abdominal wall, as required to maintain maximum continuous compression, proved satisfactory. Frequently the patient's own laced, abdominal support, firmly applied, proved equally efficacious.

Determinations of blood pressures and pulse rates did not bear out our early expectation that the headache was invariably associated with orthostatic hypotension and/or tachycardia. While all patients who exhibited orthostatic hypotension and/or tachycardia did develop headache, a considerable number (almost 50 per cent) complained of headache on the third or fourth postpartum day without evidence of a definite fall in blood pressure or marked rise in pulse rate. The essential point of practical application is that firm abdominal compression was efficacious in relieving the headache in either category.

It should be mentioned that a small incidence of postpartum headache and orthostatic hypotension and tachycardia are found irrespective of the use of spinal anesthesia. Chronic sinusitis, dental disorders, constipation, neuralgia, migraine, breast disorders, psychic, and other factors require differentiation in our experience. If spinal anesthesia be administered to patients in this group, the headache may be erroneously attributed to the anesthetic. If headache develops, firm abdominal compression should be applied in any case; and the headache, if it be of spinal anesthesia origin, will almost always be effectively

3. A higher headache incidence in vaginal, as compared with abdominal, deliveries and various gynecologic operations indicated that there were factors conducive to its production in vaginal deliveries.

4. A case of unusually severe and persistent postlumbar puncture headache exhibiting orthostatic hypotension and tachycardia was effectively relieved by firm abdominal compression. This case initiated investigation of the cause and treatment of this type of headache.

5. The routine investigation adopted in all cases of headache is outlined.

6. Over 50 per cent of patients developing headache exhibited orthostatic hypotension and/or tachycardia, but the intensity of headache bore no direct relationship to the degree of hypotension and/or tachycardia.

7. A many-tailed abdominal binder or other form of firm abdominal support proved equally efficacious in the relief of the headache.

8. Almost 50 per cent of the patients who complained of headache exhibited no evidence of orthostatic hypotension and/or tachycardia. Firm abdominal compression relieved the headache in this group also if it was of spinal anesthesia origin.

9. Causes of headache other than spinal anesthesia are enumerated. The therapeutic effect of firm abdominal compression may be utilized in differential diagnosis.

10. The two factors responsible for the headache are: first, and more important, the sudden release of intra-abdominal pressure following delivery, superimposed on the action of the anesthetic; and second, spinal fluid leakage. The mechanism of both factors is discussed.

11. The inefficacy of various drugs and local massage is noted.

12. The prophylaxis of postpartum spinal anesthesia headache is given.

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abdomen by the examiner gives most dramatic and instantaneous relief. This tentative test is important, for it indicates that maintained firm abdominal compression will successfully alleviate the headache by disengorging the splanchnic pool, correcting the cerebral circulatory imbalance, cushioning the brain, and thereby relieving irritation of the pain-sensitive structures anchoring it to the cranium. It is our belief that the increased return of blood following abdominal compression raises the pressure in the right auricle which, in turn, is transmitted via the jugular veins to the intracranial veins, thereby lifting the brain from its compressed position on the cranial floor. Traction on the pain-sensitive structures is removed and the headache is relieved.

Ephedrine, benzedrine, gynergen, aspirin, codeine, and other drugs which were tried early in this study, proved of little value and were soon discarded. No relief has been observed from massage of the head or neck, a measure which others have found efficacious.⁵ That splanchnic dilatation induced by procaine is not the sole factor causing the headache is apparent in those instances of headache which follow simple diagnostic tap. Contrary to a recent report⁶ we have observed headaches after nupercaine, and these were also relieved by abdominal compression.

Our explanation of the markedly lesser incidence of headache in cesarean section and other laparotomies is the compression of the abdomen maintained by the surgical dressing, and the more firmly it is applied, the more effective will it be in preventing headache. It is noteworthy that following hemorrhoidectomy after which no postoperative abdominal pressure by the dressing is applied there is for the same reason a higher incidence of spinal anesthesia headache than after laparotomy.

The headache may be frontal, temporal, or occipital. Throbbing in the head is produced or accentuated on sitting or standing. Sometimes the main complaint is stuffiness in the ears. In other cases, there is little headache but stiffness in the nape of the neck or shoulder muscles predominates due to traction on the upper cervical nerves. The therapy suggested has been effective in all types of complaint.

Our prophylactic orders for headache post partum consist of (1) immediate postpartum application of a medium sized sandbag to the abdomen, (2) firm abdominal binder twenty-four hours post partum to be reinforced by folded towels, particularly in the scaphoid abdomen. Frequent resetting of the binder to maintain firm pressure as the abdomen involutes or the patient shifts position is essential for effective results. It is advisable to continue the use of the binder until the patient is discharged from the hospital on the seventh to the tenth day.

Summary

1. The increasing use of spinal anesthesia in obstetrics renders timely the suggestions to be offered for alleviation of post lumbar puncture headache.

2. A headache incidence of 15 per cent was noted in a series of 300 obstetric cases after low spinal or saddle block procaine anesthesia.

Operative Findings.—Operation was done Aug. 5, 1946, under spinal anesthesia. A posterior vaginal incision and perineotomy was needed to gain enough operating room in the nulliparous tight vagina. The fibroid filling the vaginal vault was seized, morcellated, and then resected at its uterine base with long scissors. Uterine cavity and vagina were antisepticized and the cervix closed. Vaginal hysterectomy was completed with moderate difficulty, for the left uterine artery escaped briefly when its ligature was inadvertently cut by the vault-suturing needle. The posterior vaginal and perineal incisions were closed.

While mobilizing the bladder preceeding the hysterectomy, no alteration was noted in the usual fixation of bladder to cervix by endopelvic fascia, nor in the clear development of the pubocervical ligaments after upward displacement of the bladder. There was no increase in bladder base vascularization nor difficulty in lateral separation of the bladder from the broad ligaments. When the bladder was retracted and displaced higher and away from the lower uterine segment, a few rather tough adhesions near the left broad ligament base were encountered. The vesicouterine fold was somewhat higher than ordinary, but not of notable concern in the operative procedure.

Comment.—From this case, it is evident that in a supravescical extraperitoneal cesarean section, the fascial dissection and incision neither involved nor impaired the bladder-fascial support, but were confined to the enveloping layers or fascia propria of the bladder itself. Likewise, such fascial incisions as are made over the lower uterine segment are well removed from any endopelvic fascial supports. Therefore, in subsequent operative procedures requiring mobilization or utilization of the supporting ligaments, as in vaginal hysterectomy, there would be no involvement or alteration of these structures, nor disturbing interference with the operation itself.

Follow-up Note.—The patient was re-examined on Jan. 27, 1947. A very firm nulliparous introitus was noted, with a deep vaginal vault and strong posterior wall repair. Examined standing and straining, there was no weakness of the anterior and posterior vaginal walls nor of the vaginal vault.

A case is reported of vaginal hysterectomy, subsequent to two supravescical extraperitoneal cesarean sections. Such cesareans require incisions and dissections in the enveloping visceral endopelvic fascial tissues, but not of the supporting portions of the endopelvic fascia. Vaginal hysterectomy done for subsequent tumorous degeneration determined that the supporting fascia and ligaments of the endopelvic fascia were unaltered and uninjured by the previous extraperitoneal operations. No significant change in relationship of bladder and uterus occurred. Previous extraperitoneal cesarean section should not be considered a contraindication for vaginal hysterectomy.

VAGINAL HYSTERECTOMY SUBSEQUENT TO EXTRAPERITONEAL CESAREAN SECTIONS

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SOME unusual aspects provide the interest in which the following case is reported. Anatomic data is given on pelvic fascia as found at vaginal hysterectomy some four years after a second extraperitoneal cesarean section. The vaginal approach provided new observations to the writer and more clearly defined certain statements hitherto regarded as probably true.

The past history was of especial interest in the light of subsequent findings. This patient was first seen on June 21, 1940. She had been in labor for twenty-nine hours, membranes ruptured thirty-six hours, and the fetal heart sounds had not been heard for four hours. The fetal head was dipping but unengaged, the cervix thick, dilated 5 cm., and a foul vaginal discharge was evident. The patient was exhausted, with rapid pulse, temperature 101.4° F., and in very severe labor. She was given sedation, fluids intravenously, chemotherapy, a transfusion readied, and after a period of six hours a supravescical extraperitoneal section of the Waters' type performed. A large stillborn fetus was delivered. Despite a transient infection at the drain site, she recovered rapidly.

On March 30, 1941, she had a spontaneous two months' abortion. She was referred again for care in October, 1941. Examination showed a normal two months' pregnancy. Her pelvis was considered a small android type, subsequently confirmed by x-ray. Elective section was done on May 21, 1942, one week before term. A Waters' type extraperitoneal cesarean section was chosen to determine its feasibility as a repeat operation. Moderate difficulty was encountered from the previous operative adhesions in the retrovesical area, but operation was completed without complication in forty minutes. The drain was removed in forty-eight hours, she was up on the eighth day, and discharged from the hospital on the eleventh postoperative day.

The first notation of symptoms which eventuated in vaginal hysterectomy was on Aug. 17, 1945. This 40-year-old patient had been having terrific labor-like menstrual cramps for six months. Menstruation lasted five days and was regular, but the flow was heavy and clotted. Examination showed a tight nulliparous-type introitus and vagina, a small, closed, clean cervix, and a moderately enlarged uterus with a golf-ball sized intramural fibroid. Hysterectomy was advised on the basis of the findings and symptoms.

She was next seen eleven months later, stating that all pain had stopped several months after the last visit but the menstrual flow had become extremely heavy, prolonged from ten to eighteen days, and associated with the passage of large clots.

Examination now disclosed a vaginal vault filled with a large fibroid, 10 cm. in diameter, prolapsed through a dilated cervix, with the uterus comparable in size to a two months' pregnancy and containing other small fibroids. She was markedly anemic, with a hemoglobin of 50 per cent and 2.3 million red blood cells. Prompt operation was clearly needed.

Alternative measures were vaginal myomectomy followed at a later date by an abdominal hysterectomy, or vaginal myomectomy-hysterectomy with suitable precautions.

perman and Greenblatt⁷ were unable to confirm the findings of Farris in males and nonpregnant females, and objected to the subcutaneous avenue of injection by Farris and Zondek in judging the accuracy of the two-hour rat test. Kupperman and Greenblatt,⁷ too, noted the test to be only 65 per cent accurate with the subcutaneous injection, but obtained excellent results with the intraperitoneal route. However, Salmon¹⁵ states that the accuracy is 95 per cent at two hours with the subcutaneous injection.

Purpose and Procedure

The purpose of the study was to determine the reliability of the two-hour rat pregnancy test as a routine procedure for the average laboratory. The two-hour rat test was performed on each of 228 specimens of urine sent to the Endocrine Laboratory of the Jefferson Hospital in 200 ward, clinic, and private cases, for a Friedman pregnancy test. A total of 390 rats was used and examined before the Friedman tests were completed. Rat tests with one rat were performed in the first 124 cases, and the Friedman tests awaited. If there was a discrepancy with the Friedman test, or a doubtful reaction, additional rats were used. In the suspected ectopic pregnancy cases two or three rats were used, and this number of animals was routinely employed later in the study. Two rats were used with each specimen in a comparative study of the two-, six-, and twenty-four-hour rat tests. One rat was opened in two hours and the other in six or twenty-four hours. A clinical diagnosis was obtained for corroboration four to nine weeks later in 195 of the 200 cases.

Technique.—The technique followed in the two-hour rat pregnancy test was that advised by Kupperman and Greenblatt.⁷ Immature albino female rats 21 to 30 days of age, and 30 to 60 Gm. in weight were used. While the rat was held posteriorly 2 c.c. of an unaltered morning specimen of urine was injected intraperitoneally in divided doses of 1 c.c. each into the right and left lower abdominal quadrants. Two hours later the animal was killed by ether asphyxiation. At autopsy the intestines were displaced, and the ovaries readily exposed. The test was considered negative if the ovaries were pale or pinkish—and positive if one or both of the ovaries were light to dark crimson. The six- and twenty-four-hour tests were modified in that an intraperitoneal, rather than a subcutaneous route of injection, was used.

Results and Discussion

Normal Intrauterine Pregnancy.—In the 87 normal intrauterine pregnancies there were three errors in the Friedman tests, and four errors in the rat tests—giving an accuracy of 96.4 and 95.4 per cent, respectively, (Table I). The errors in the Friedman and rat tests occurred in different cases so that if one was incorrect, the other was correct. Using other specimens four to eight days later, three of the errors, one rat and two Friedman tests, were corrected. In three cases positive tests were noted seven days after the expected date of the first missed menses.

Ectopic Pregnancy and Abortion Cases.—Variances between the Friedman and rat tests were noted in the group of 35 clinically proved cases of disturbed pregnancy—such as abortions, ectopic pregnancy, and intrauterine fetal death (Table I). There were no false positive or negative rat tests, but there were four false negative Friedman tests, of which three occurred in the abortion and one in the ectopic pregnancy groups. Zondek⁴ stated that the rat hyperemia test is especially sensitive for the diagnosis of pregnancy, since the test is evoked with one-third of the pregnancy urine gonadotropin that is necessary for luteinization (Aschheim-Zondek test). It would seem, therefore, that the rat test would

AN EVALUATION OF THE TWO-HOUR RAT TEST FOR PREGNANCY*

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THE first accurate pregnancy test was not available until Aschheim and Zondek made their basic observations on gonad stimulating substances in pregnancy urine¹ and in 1928 proposed the pregnancy test² which bears their name. Certain disadvantages of this highly accurate biologic hormone pregnancy test caused the originators^{3, 4} and others⁵ to describe tests that were shorter, more convenient, or more applicable for the average laboratory. Of these tests, the Friedman rabbit and Hogben frog tests are the most widely used today. The inconveniences of these two tests and the objections to the test animals led more recently to the proposal of the rapid rat ovary hyperemia pregnancy test. The rat as a pregnancy test animal offered numerous accepted advantages in care and cost as well as that of increased sensitivity to gonadotropins.⁶

The positive end point of the test, hyperemia of the ovary, is the first gonadotrophic reaction to appear after the parenteral administration of the urine of pregnant women, and is noted suitably in the rat ovary only.^{4, 7} This reaction appears in two hours and persists for thirty-six hours. Furthermore, hyperemia of the rat ovary has been reported⁷ to be present after the administration of luteinizing and luteotrophic gonadotropins but not after the use of the follicle stimulating hormone.

The advocates of the rapid rat pregnancy test have shortened the time from thirty-six to two hours, and have maintained with few exceptions an accuracy close to 100 per cent. In 1931, Eberson and Silverberg⁸ reported a rapid rat-ovary pregnancy test at thirty-six and twenty-four hours with the subcutaneous and intraperitoneal injections of a urine extract. Reiprich,⁹ the Walkers,¹⁰ and Kelso¹¹ used unconcentrated urine and observed favorable results at twenty-four and thirty hours. The results of Frank and Berman¹² at twenty-four hours were comparable with the Aschheim-Zondek test and better than the rabbit test. They were accurate at eight hours, and later¹³ were obtainable in four hours. Salmon and his co-workers¹⁴ described a six-hour test which was correct in 108 of 109 cases. Salmon stated in a personal communication¹⁵ that the test was positive in two hours in 95 per cent of the cases. The six-hour test was found by other investigators to be simpler than,¹⁶ comparable to,¹⁷ and as reliable¹⁸ as the Friedman test. Kupperman and his co-workers¹⁹ in 1943 and later^{7, 20} reported a 99.5 per cent accuracy with a two-hour rat test in which they favored the intraperitoneal over the previously used subcutaneous route of injection to allow more complete and rapid absorption of the gonadotropins.

However, Farris²¹ found the two-hour rat test to be positive in some males and nonpregnant females. Zondek⁴ compared the two-, six-, and twenty-four-hour rat tests, and reported the two- and six-hour tests to be inaccurate. Kup-

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Farris²¹ reported false positive rat pregnancy tests in some males and non-pregnant females. The present series included the menopausal and psychoses cases in which Farris noted false positive rat tests. Others were unable to confirm the findings of Farris in males⁷ and in females at midcycle.^{7, 12}

Comparison With Six- and Twenty-four-hour Rat Tests.—In a small series of 47 cases the two-hour rat test compared favorably with 39 six-hour, and 8 twenty-four-hour rat tests. The two- and six-hour rat tests each had three false negative tests, while there were two in the twenty-four-hour tests. If the two-hour test was incorrect, the six- or twenty-four-hour test was correct and, if either of the latter was incorrect, the two-hour test was correct.

Toxic Reactions.—The rat is more tolerant to toxic specimens of urine than is the rabbit. Five rabbits and two rats died as the result of toxic specimens for percentages respectively of 2.2 and 0.8. Ramsey¹⁸ noted toxic reactions in 3 per cent of the rabbits, and 0.5 per cent of the rats. In considering possible repetition of tests, it was noted that there were doubtful reactions in 2.3 per cent of the rabbits and 5 per cent of the rats.

False Negative and Doubtful Reactions.—Two rats were used for each test by others. These studies suggest the need for three rats per test due to the number of false negative and doubtful reactions. The use of three rats increases the cost to approximately that of the rabbit test, and decreases the simplicity of the test. One rat was used initially in 124 cases, but 24 tests were repeated because of thirteen doubtful reactions three slow responses in the positive group and eight variations with the Friedman test. In the group of eight variations, there were correctly two positive and six negative rat tests, in contrast to two negative and six positive Friedman tests. In each repeat test, urine from the original specimen was injected into two rats. On repetition the three positive slow responses remained positive, while in the group of thirteen doubtful reactions there were two positive and eleven negative tests. In the group of eight tests which had varied with the Friedman tests, the two positive rat tests remained correctly positive. Three of the six false negative rat tests persisted as false negative. The other three false negative tests were positive on repetition. In two of these three positive cases, four of the six rats failed to respond.

In a group of 55 cases, two rats were used per test. There were no false tests, but nine rats failed to react in 33 positive cases. Three rats were used in each of 21 cases of possible ectopic pregnancy. The rat test was correct in all. In the fifteen positive cases there were fourteen false negative and four doubtful reactions. As many as six of these cases may have been added to the error group if only two rats had been used. Therefore, with the advised use of two rats, the error group with three rats may have been increased by 200 per cent to give a very unsatisfactory percentage of accuracy.

As noted by others^{7, 12, 14, 15, 19, 20} when the rat test reaction was positive, it was conclusive. However, negative reactions were inconclusive. The percentage of false negative rats was high. While in other series^{7, 12, 15} the number ranged from 0.2 to 3.8 per cent, it was 10 per cent in this group of 390 rats. The 40 false negative and 20 doubtful reactions were 15.4 per cent of all rats used. The 40 false negative reactions occurred in 23 per cent of the positive cases and were equally distributed between 13 cases of normal intrauterine pregnancy and 14 cases of complications of pregnancy. Of all negative reactions, 19 per cent were false. As a result, there was a feeling of uncertainty in reporting negative reactions and tests.

Interpretation of the Test.—Another point of difficulty involves the reading of the test. The test ovaries vary in color so that Kline¹⁶ has listed four negative, one doubtful, and four positive shades while Farris²¹ noted six variations. The typical crimson positive and pale negative are distinct. However, the shades between these are difficult to interpret and may be responsible for a false reading.

TABLE I. —COMPARISON OF THE TWO-HOUR RAT AND FRIEDMAN PREGNANCY TESTS

| FINAL CLINICAL DIAGNOSIS | NUMBER | FRIEDMAN | | RAT | |
|-----------------------------|--------|----------|----------|----------|----------|
| | | POSITIVE | NEGATIVE | POSITIVE | NEGATIVE |
| Normal pregnancy | 87 | 80 | 3* | 83 | 4† |
| Ectopic pregnancy | 8 | 5 | 1‡ | 8 | 0 |
| Threatened abortion | 12 | 7 | 2‡ | 12 | 0 |
| Incomplete abortion | 10 | 1 | 8§ | 2 | 8 |
| Intrauterine fetal death | 5 | 3 | 2 | 2 | 3 |
| Nonpregnant | 78 | 0 | 75 | 0 | 78 |
| Totals | 200 | 96 | 91 | 107 | 93 |

*Two repeat specimens positive.

†One repeat specimen positive.

‡False negatives.

§One false negative.

be of especial value in those cases of disturbed pregnancy in which the gonadotropin levels were low. However, Zondek⁴ further stated that the rat test is adequately accurate for the determination of cases of undisturbed pregnancy, but insufficient for cases of disturbed pregnancy. He reported inaccurate results with the two-hour rat test in four cases each of ectopic pregnancy and abortions.

As a rapid diagnostic test for pregnancy, the two-hour rat test attains its purpose as an aid in the detection of ectopic pregnancy. This fulfills the wish of the clinician who cannot wait for one of the more time-consuming pregnancy tests, but who wishes confirmation of his diagnosis by a pregnancy test. There were 28 cases in which ectopic pregnancy was considered as the primary diagnosis. This was the final diagnosis in eight cases, as confirmed by operation. The rat test was correct in these proved cases, while the Friedman test was incorrect in one case (Table II). In this group of 28 cases, the Friedman test alone would have been misleading and time consuming. In the 24 cases in which Friedman tests were done, there were two false negative tests in the ten cases of disturbed pregnancy, and two doubtful tests in the twelve nonpregnant cases. Kupperman and Greenblatt⁷ reported an 88.3 per cent accuracy with the two-hour rat test in eighteen cases of ectopic pregnancy.

TABLE II. COMPARISON OF FRIEDMAN AND TWO-HOUR RAT PREGNANCY TESTS IN POSSIBLE ECTOPIC PREGNANCY CASES

| FINAL DIAGNOSIS | NUMBER OF CASES | FRIEDMAN | | RAT | |
|---------------------------------------|--------------------|----------|----------|----------|----------|
| | | POSITIVE | NEGATIVE | POSITIVE | NEGATIVE |
| Ectopic pregnancy | 8 | 5 | 1* | 8 | 0 |
| Pelvic inflammatory disease | 8 | 0 | 8 | 0 | 8 |
| Abortions | 4 | 1 | 3‡ | 2 | 2 |
| Fibroids | 2‡ | 0 | 1 | 0 | 2 |
| Menstrual disturbances (Endocrine) | 4‡ | 0 | 3 | 0 | 3 |
| Intrauterine pregnancy | 2 | 2 | 0 | 2 | 0 |

*False Negative.

‡One False Negative.

‡One Doubtful Friedman—not repeated.

Nonpregnant Cases.—The rat and Friedman tests were negative in the 78 nonpregnant cases. The nonpregnant cases included diagnoses of menopause, pseudocyesis, endocrine menstrual disorders, psychoses, fibroids uteri, pelvic inflammatory disease, ovarian tumors, and carcinoma of the genital tract. This group included the types of cases in which Zondek¹³ noted and in which Greenhill²² stated that false positive pregnancy tests may occur.

A METHOD OF DELIVERY FOR HYDROCEPHALUS ASSOCIATED WITH BREECH PRESENTATION

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THE method to be described was suggested by a description in Stander's *Obstetrics*,¹ and differs from this only in minute detail. It is therefore presented not because of originality, but rather because its extreme simplicity and safety warrant for the procedure a more general acceptance than it has received. A recent case is the impetus for this report.

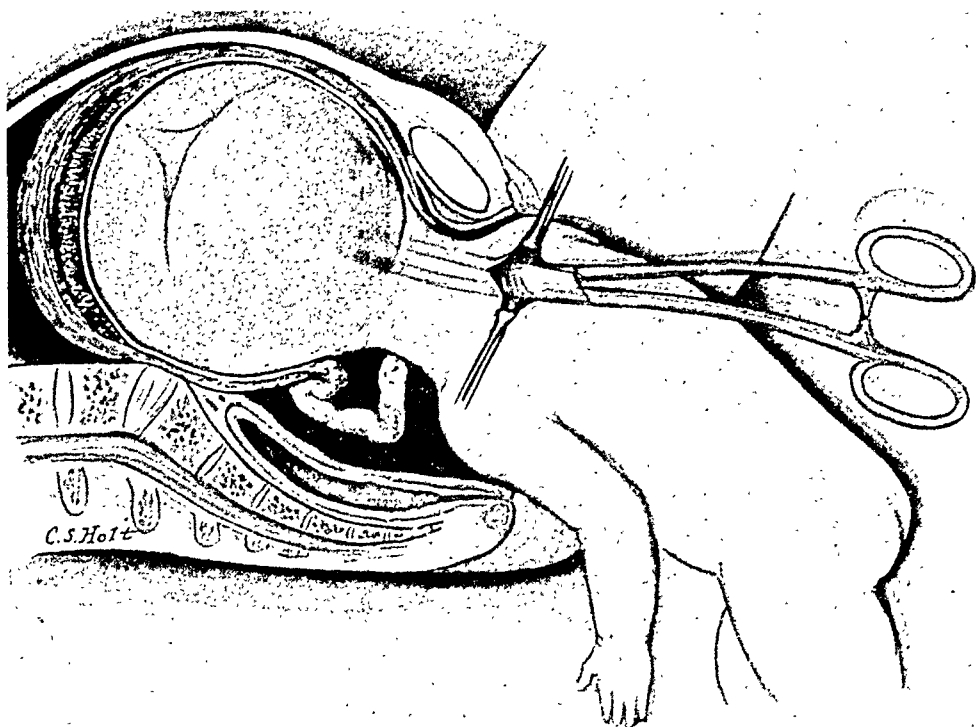


Fig. 1.

Method of Delivery.—If the case is one of frank breech, the breech is allowed to advance and is delivered according to accepted procedure, with one exception: since the labor is to end by stillbirth, it is permissible to spare the patient the necessity of delivering the breech by voluntary effort. This may be accomplished, when the breech approaches the perineum, by making traction in the groin with a blunt hook. Delivery of the breech and of the shoulders is then completed as under ordinary circumstances. No attempt is made to cause the head to engage more deeply. A Jackson retractor is placed anteriorly, and the highest spinous processes which one can visualize are palpated. An incision is made in the midline over two of these processes, which ordinarily are those of the lower cervical or upper thoracic spine. The skin edges are retracted by Allis forceps, and a laminectomy performed over these two segments. (This is readily accomplished in the fetus by incision through

Conclusions

On the basis of this series, the two-hour rat pregnancy test is noteworthy because of:

1. The rapidity with which the result may be obtained.
2. The increased sensitivity of the test as noted by the accuracy in cases of disturbed pregnancy.
3. The rarity of false positive tests.
4. The increased tolerance of the rat to the toxic specimens of urine.
5. The conveniences of the test and the test animals.

However, further investigation is necessary to:

1. Further increase the accuracy of the test since it ranged below the Friedman test in normal intrauterine pregnancies.
2. Obviate the large number of false negative and doubtful reactions which caused a feeling of uncertainty in reporting negative tests.
3. Increase the color intensity of positive reactions.
4. Lessen the need for three rats per test.

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FULL-TERM PREGNANCY FOLLOWING OPERATION FOR CONGENITAL ABSENCE OF VAGINA*

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ANOMALIES of the genital tract are always of interest. Some of these anomalies may be associated with primary amenorrhea and sterility, particularly when there is nonunion of the Müllerian system with the ectodermal vaginal inpouching. The imperforate hymen is the simplest of the defects encountered in this group. More or less complete absence of the vagina, even in the presence of a functioning uterus, as evidenced by hematometra, is not unusual. A connection can always be established surgically between uterus and vulva, and usually coitus can be made possible. However, the subsequent occurrence of pregnancy following such surgical procedures is extremely rare. Only two reports of such an event have been found in the literature. In one¹ a cavity was created between the rectum and the bladder. Skin flaps from the thighs and labia were used for lining this cavity. The patient became pregnant and was delivered at term by cesarean section. In the second report² a segment of sigmoid was interposed between the uterus and the vaginal pouch. The patient was delivered spontaneously of three children, the last weighing 4,500 grams.³

The present report concerns a patient who was first seen in 1937 at the age of 16 years, complaining of primary amenorrhea. Her identical twin sister had been menstruating normally for approximately two years. Examination revealed a complete atresia of the upper two-thirds of the vagina. The lower pole of a palpable abdominal mass was separated from the apex of a small vaginal pouch by a distance of 5 to 6 centimeters. The mass, approximately the size of a sixteen-week pregnancy, was interpreted as being a dilated uterus containing retained menstrual blood. Under anesthesia, the tiny vaginal vault was split transversely and by blunt and sharp dissection a cavity was created between the bladder and rectum. The lower pole of the mass was incised and approximately twelve ounces of retained black menstrual blood escaped. The uterus was then anchored to the vaginal pouch with mattress sutures. Recovery was uneventful and normal menses followed. Postoperative examination revealed a short, narrow vagina with the lower pole of the uterus flush with the vault. No vaginal cervix existed.

This case was previously reported by one of us (Baer) before this Society on Dec. 17, 1937.

The patient married in 1941. Conception followed the elimination of contraception in 1946. Pregnancy progressed uneventfully and, since there was neither detectable cervix nor a detectable cervical os in the vaginal vault at term, an elective cesarean section was performed. She was delivered of a normal 7 lb., 15 oz., male by laparotrachelotomy. At operation, a well-formed lower uterine segment was found, and the pelvic genitals were normal in all respects except for very superficial tortuous ovarian arteries coursing along the infundibulopelvic and upper broad ligaments. After the contents of the uterus had been evacuated and the bleeding controlled, the cervical canal was located and readily dilated to number 10 Hegar. Postoperative convalescence was uneventful.

*Presented before the Chicago Gynecological Society, Feb. 21, 1947.

the laminae with a scalpel, and removal of the fragment with a small rongeur.) The tip of a uterine dressing forceps—which is considered as preferable to the catheter as mentioned in the original description—is introduced into the opening in the spinal canal and forced gently but firmly upward into the cranial cavity. It is rotated to enlarge the canal, and the blades are separated slightly. By making pressure upon the head from above, cerebrospinal fluid is caused to issue from the laminectomy wound. This is continued until either the flow of fluid stops, or the collapsed head advances sufficiently that it can be delivered. The dressing forceps is now withdrawn, and the head delivered by the Mauriceau maneuver.

The procedure is simplicity itself. Since it is done under direct vision without possibility of injury to the maternal soft parts by bone spicules, it is considered as preferable to the more popular approach with the customary perforator behind the ear or through the lamboidal suture.

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BILATERAL SIMULTANEOUS TUBAL PREGNANCY

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BILATERAL tubal pregnancy is infrequent, for a total number of 84 authentic cases have been reported since 1890, up until and including 1945. A survey of records at the hospital with which I have been affiliated for the past twenty-five years has no incidence of any case of bilateral tubal pregnancy during that time.

D. B., aged 35 years, a married white woman, consulted me on Dec. 6, 1946, complaining of vaginal bleeding and pelvic pains. The bleeding began about three weeks prior to consultation, although she ignored it and continued working. About November 29 her pains became more annoying, colicky in type, and of short duration, although she rested comfortably at night. From the time of the onset of bleeding until November 29 most of the time she was without pain, but continued to have vaginal spotting. About five days before I saw her, the pains became more severe, also the bleeding at times was on the increase. Her menses were always regular, occurring every 28 days and lasting 7 days, with occasional premenstrual cramps. She had had one normal delivery in 1934. Her general health was always good. A thyroidectomy was done in 1940. Since then she had been more or less nervous. Examination of this patient revealed that she was acutely ill with a temperature of 99° F., pulse rate of about 90, and respiration 22. Extreme tenderness was elicited on palpation over the entire lower abdomen, more marked in the right lower quarter, and intensified on deeper palpation and percussion. Vaginal examination revealed very little; the cervix was soft, but, due to increased discomfort, it was impossible to do a thorough examination. The patient agreed to be hospitalized for further study. She was admitted to the hospital in the afternoon on the same day. The temperature on admission was 99.2° F., pulse 90, respiration 22, blood pressure 110/70. Urinalysis: acid, sp. gr. 1030, albumin trace, sugar negative. Microscopically: hyaline casts, loaded, granular, many. Complete blood count hemoglobin, 83 per cent; red blood cells 4,400,000; white blood cells, 11,000; C. I., 0.94; differential band, 13 per cent; neutrophils, 62 per cent; lymphocytes, 25 per cent. During the night the patient rested comfortably. The following morning a repeat blood count was hemoglobin, 66 per cent, red blood cells, 3.85; white blood cells, 15,600; band, 17 per cent; neutrophils, 71 per cent; lymphocytes, 12 per cent. Preoperative diagnosis of ruptured right tubal pregnancy was made. All preparations for blood transfusion and plasma were instituted. Under spinal anesthesia a midline suprapubic incision beneath umbilicus was made. Considerable amount of free blood with clots was found in the abdominal cavity. The right tube was involved in the outer third, considerably distended, and bleeding from the fimbria with placental tissue showing at the opening. The tube was carefully released from its adherence to the ovary and removed with cornual resection. The left tube was considerably distended at its outer third, but sealed at the fimbria. This was also removed with cornual resection. During the operation the patient received 1000 c.c. of saline with 5 per cent glucose. The time of operation consumed twenty-eight minutes. Upon returning to her room she was given 500 c.c. of plasma.

Pathologic Report.—Specimen consisted of both tubes and a small mass of spongy placental-like tissue. The fimbriated end of one tube revealed the

The simple primary operative procedure described here served several very useful purposes: (1) it provided an outlet for menstrual blood; (2) it provided a canal for coitus, and (3) it made impregnation possible.

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SIMULTANEOUS TUBAL ABORTION AND UTERINE PREGNANCY

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THE concomitant existence of uterine and tubal pregnancy is rare. Parry¹ states that out of 500 cases of tubal pregnancy 22 were simultaneous with uterine pregnancy. He called such a condition as combined pregnancy in contradistinction to the term compound pregnancy which is applied to cases of intrauterine pregnancy superimposed on a previously existing ectopic pregnancy that has terminated in lithopedion formation.

On summarizing the cases in the literature as published successively by Novak² in 1926, Gemmel and Murray³ in 1933, Mathieu⁴ in 1937, Ludwig⁵ in 1940, and Howard⁶ in 1945, there are 356 and, with the addition of the present case, presented for the first time in the Philippines, the total up to 1946 is 357 cases.

Double ovum twins are of frequent occurrence in uterine pregnancies. This may explain the existence of concomitant tubal and uterine pregnancies; the difference of the two conditions being only in that one ovum is implanted in the tube and the other in the uterus. But since the site of implantation is different, one being tubal, and the other uterine, the time of impregnation must also be different. In other words such a combined pregnancy must be the result of superfecundation or the impregnation of the ova on different occasions. When the uterine pregnancy is older than the extrauterine one, the difference of the two at the most is less than three months. The reason for this is that at the end of three months the uterine cavity becomes obliterated by the close application of the decidua capsularis with the decidua vera rendering impossible the uterine passage of the spermatozoon. The uterine pregnancy can be over three months older than the extrauterine pregnancy only if the extrauterine pregnancy fails to grow and causes no abnormal symptoms while the uterine pregnancy proceeds in its development towards term. The usual fate of a tubal pregnancy, however, is that it ends in either tubal abortion or tubal rupture long before it reaches the third or fourth month.

For the reasons given above, it is hard to explain the great discrepancy of age of the case reported by Clarke⁷ and the one reported by Moudry and associates.⁸ In Clarke's⁷ case, the tubal pregnancy was two months old while the uterine pregnancy was at term. In Moudry's⁸ case the tubal pregnancy was five weeks and the uterine pregnancy was eight months. Both cases presuppose that the tubal impregnation took place when the uterine pregnancy had advanced to at least six months long after the complete obliteration of the uterine cavity rendering impossible the ascent of the spermatozoon. The only explanation possible is either that the spermatozoa can live many months in the pelvic cavity or in the tube and impregnate later, or that the tubal pregnancy became arrested in its growth and failed to show signs of rupture until after many months. Either event, if possible, is indeed very unusual.

Case Report

L. A., 30 years old, was admitted to the Philippine General Hospital on Sept. 11, 1945, because of hypogastric and lumbar pains, slight vaginal bleeding, the general weakness.

She had had ten pregnancies, all ending in full-term deliveries. The last child was 2 years and 9 months old at the time.

presence of a protruding saclike structure in which there was a tiny rent. The lumen was found to be dilated. The fimbriated end of the other tube was congested, and there was some spongylike material present which covered the lining.

Microscopic examination of a section of tube revealed a marked thickening of the walls due to fibrosis, fatty infiltration, and edema. The mucosal papillary structures were flattened and markedly distorted. There was a moderate infiltration of the mucosal papillary structures with lymphocytes. Another section of tube showed considerable distortion of all the normal histologic structures and an infiltration of the walls with decidual cells. There were also a few well-defined chorionic villi present. A section of tissue expressed from the tube revealed it to be definitely placental in character. It was made up of large edematous appearing chorionic villi.

Diagnosis: Bilateral tubal pregnancy. The patient's postoperative course was uneventful. She was discharged from the hospital on December 17 and classified as recovered. Subsequent to her leaving the hospital, she was seen at her home, and also at my office on Jan. 6, 1947, and her last office visit was Feb. 3, 1947, at which time she was fully recovered.

Special Article

AN OUTLINE OF THE CONDUCT OF PHYSIOLOGICAL LABOR*

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WHEN parturition is neither inhibited nor disturbed by mechanical, chemical or psychological factors it may be termed physiological labor.

All interference when there is no inhibitory or disturbing factor superimposes a pathologic state upon a physiologic function.

Mechanical and chemical abnormalities are observed and treated according to the principles of good obstetrics—such conditions are relatively rare. Psychological and therefore psychosomatic aberrations are seldom diagnosed or treated before or during childbirth. They complicate the large majority of labors. They are the direct cause of interference in 90 to 95 per cent of maternity cases, thereby being responsible for much maternal and infant morbidity and some mortality.

Physical injuries sustained during labor are carefully repaired because it is recognized as essential for the future health and marital happiness of the woman. Psychological injury sustained during labor is neither avoided nor repaired, yet it is not generally recognized that, because of this obstetric oversight, the future health and marital happiness of thousands of women are being destroyed every year. By consideration for the psychosomatic aspects of labor, maternal morbidity is decreased mainly because interference is minimized. The decline in infant morbidity is appreciable, and is largely due to the fact that forceps operations, deep narcosis, and prolonged anesthesia are seldom required for delivery of the child. Physiologic mothers, with few exceptions, insist upon breast feeding their babies—a conscious sense of achievement and pride makes childbirth an event to be repeated and not avoided. One or two child “families” are unsatisfying, for these women and the absence of frustration or feeling of “having let her child down” enables a normal development of the instinct and philosophy of motherhood which in turn stabilizes family life upon which the future progressive development of human society depends.

What are the procedures that we employ to enable a woman to have her child in this way? It is necessary that a woman should not be just a passive subject for treatment but a properly prepared and educated collaborator in the birth of her child; therefore, at the time when labor starts she will have been prepared by understanding the signs and symptoms of commencing labor. She will have been told that the boredom of the last fortnight is normal and

*Presented by invitation, at a meeting of the Maternity Center Association, New York Academy of Medicine, January 17, 1947.

Her last menstrual period occurred in the latter part of May, 1945. In July she had morning sickness in the form of nausea and vomiting. In the middle part of August she had slight vaginal bleeding for three days. And for the last nineteen days she has been having abdominal and lumbar pains and general weakness.

Her mother died of pulmonary tuberculosis.

Physical examination showed impairment of breathing over the right interscapular and base regions, muscular rigidity and tenderness over the lower abdomen, specially on the right side. The fundus uteri could be palpated two fingerbreadths above the symphysis. Vaginal examination showed the uterus to be enlarged to the size of two months' pregnancy, and at the right fornix could be felt a tender sausage-like mass.

The diagnosis on admission was pregnancy at 2 months complicated by acute salpingitis of the right tube. So she was given sulfonamides, bromides, and vaginal douches. Her abdominal pains improved, but suddenly on the ninth day after such treatment she had acute abdominal pain and much tenderness in the somewhat full right fornix. She was immediately operated upon.

On laparotomy, much fresh and clotted blood was found in the peritoneal cavity. The right tube was very much enlarged and congested and filled with dark clotted blood mixed with chorionic tissue which was being extruded through the infundibulum. The right ovary, left tube, and left ovary were normal. The uterus was enlarged to the size of a two months' pregnancy.

The postoperative diagnosis was tubal abortion, one month; uterine pregnancy, two months.

Except for slight vaginal bleeding on the third day which, however, subsided after two days, and a slight evening rise of temperature, her recovery was smooth, and she was discharged on the eighteenth postoperative day.

In the follow-up, however, she told us that one month after she returned home when she resumed her household activities, she aborted. Her usual menstruation reappeared one month after her abortion. She was seen in January, 1946. Her uterus then was small and completely involuted. Except for the persistence of her cough, she was in fair condition. In January, 1947, she was again examined internally. The uterus was small. Her menstrual periods continued to recur monthly and without pain. She was referred to the antituberculosis clinic for her cough, chest oppression, and afternoon rise of temperature.

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subjected to the action of forces which are beyond her control. She is still quite happy, but between the contractions it will be noticed that she is quieter and more thoughtful. Frequently a flush over her malar bones is present.

As the hours of the first stage in the primiparous labor wear on, she will recognize the necessity for and the comfort which she gains from relaxation during the contractions; at the same time the demands upon her patience and her self-confidence increase. This is purely an emotional state in the large majority of women and has little or no relationship to physical pain. By the time the cervix is three-fifths dilated there is a necessity for advice and it is, what I term, *the first testing period* of labor. At this time a woman must not be left alone. She wants companionship; she wants the reiteration of the course of labor; she wants to be told what to do. She needs reassurance in a kindly but not over sympathetic manner—this is not a time for too much sympathy but rather for firm encouragement, common sense explanation, and companionship. Point out to her that this strain upon her fears and fancies is a normal part of labor which will soon pass, but on the other hand it is an indication of progress and nothing whatever to alarm her—it is indeed what we wish and what we expect.

Naturally these signs and symptoms vary a lot in different women, but it is unusual that a well-conducted woman will fail to reconstitute her ideas on labor at this point. The first testing point can be passed easily if treated with understanding of a woman's reactions and the influences to which her mind is being subjected. This is the time when deep medication or sedation is frequently employed because of failure to understand the significance of the emotional as well as the physical changes of a woman at this stage. Tiding over the "first test" is not a difficult matter. It can be done by a nursing sister or an assistant or anyone who is present to give the necessary comfort and advice. Not infrequently the husband proves to be an excellent attendant, and labor passes on satisfactorily until between four-fifths and full dilatation of the cervix. This is the *second testing period* of labor and it is not a purely emotional change. Owing to the nature of the sense receptors, the cervix uteri during full dilation may be subjected to a tension which gives rise to referred pain over the sacral area. This is described as a backache. The onset of this backache with the increased violence of contractions is frequently a stern test for a woman having her first child. My observations upon this phase are such that I have termed it the *pain period of labor*, and in the majority of physiologic labors it is the only time during which the woman has actual physical discomfort.

This is the time when the attendant obstetrician should be present with the woman. The diagnosis of four-fifths to full dilatation is made possible by close observation of the emotional changes in a woman and may be corroborated by examination. It is the *transition* from the first to the second stage, and if this is satisfactorily conducted the whole labor will take on a different character and have a best possible chance of becoming a physiologic function. Understanding and personal attention is again required. A woman needs hand pressure or rubbing over her sacrum to comfort her. She may

reasonable but should not be taken too seriously. Consequently, when it becomes evident that her labor has started, she is pleased and not a little excited, and in that frame of mind communicates with her doctor or enters the maternity hospital.

In outlining the especial care which is necessary to obtain a physiologic labor, we must presume that all the accepted principles of good obstetrics are observed unless such principles cause emotional disturbance to a woman, in which case they should be applied in such a manner that no alarm is occasioned.

During the early stages of labor it is not necessary to keep a young woman in bed, providing that she understands how to behave when the uterus contracts. It is advisable for the attending physician to see his patient as early as possible in labor so that he can remind her of the teaching that she has had and point out to her the necessity for relaxation during contractions of the uterus. It is also an opportunity for reaffirming his confidence in her and thereby strengthening her confidence in him. At the same time it is his duty to see that her emotional attitude towards labor is sound; that she is not afraid to undertake a new and testing experience. There will be no necessity for him to stay with the patient once he has assured himself that she is capable of conducting herself satisfactorily—it is not usual that the physician need stay for more than fifteen or twenty minutes in the early stages of labor.

If, however, he wishes to stay so that he can watch all the phenomena of a normal labor and endeavor to deduce the significance of these phenomena, the picture presented to him will be very much as I propose to outline now. Unfortunately, it is not the custom to observe the phenomena of normal labor—it takes too much time, and the average scientist does prefer (and probably quite rightly) to observe abnormality rather than normality.

As the contractions continue to get a little stronger and possibly a little more frequent, so the manner of the patient gradually changes. The excited and easily laughing girl may become more serious, not because there is any undue strain placed on her, but because there are certain changes going on in her nature, probably the disposition of her blood sugar, but this has not been accurately worked out yet. The attendant must bear in mind that the first principle of his care is that the patient should not be allowed to have any anxiety or cause for anxiety, therefore his words, actions, and even his thoughts should be along lines of confidence and truth—you cannot deceive a woman in labor. She should already have become acquainted with the fundamentals upon which her own conduct must be based. She must be patient, self-controlled, and able to work when called upon. These cardinal principles upon which a woman conducts her own labor are very largely the cardinal principles upon which a woman will conduct her own life if she wishes to make a success of it, and this may be pointed out to her with advantage.

The first thing that will be noticed is that a succession of emotional phenomena, which are obviously correlated with the physical changes, occurs during the progress of labor. As the cervix dilates to about two-fifths, a woman becomes more conscious of the trial that she is undergoing; she recognizes that, although there is no discomfort attached to the contractions, she is being

She should also be instructed in the use of her analgesic apparatus, either Minnitt's gas and oxygen or trichlorethylene inhaler, and it is placed within her reach to be used if she needs it.

When the second stage contractions have become well established and the head is advancing through the birth canal, the bearing down effort may be urged and increased. During the first stage the posture of the patient is of little importance, but in the second stage a definite posture must be assumed. After considerable experiment and trial the dorsal position has been found to have advantages over any other. One pillow under the shoulder blades and two pillows under the head and neck raises her upper back to an angle of about thirty degrees to the bed. With the onset of a contraction the knees are raised and held by the woman herself, with her hands either over the knees or in the popliteal spaces—the legs are widely separated. This is the posture of open squatting, but the body weight is taken on the lower back instead of on the feet.

With the onset of a contraction, the woman is warned to take two deep breaths and not to push until the uterus pushes for her. Then she holds her breath after a full inspiration and pushes down, takes a second breath, and again exerts an expulsive influence until the contraction wears off. She then puts her legs down, shuts her eyes, takes two or three more deep breaths and relaxes completely. In this way a marked stage of amnesia is induced between the contractions, and in a semi-conscious restfulness she will lie oblivious to her surroundings and her discriminatory and discretionary senses will be lowered. Quiet peacefulness should reign in the labor ward, and noise of any sort must be avoided. Conversation should be eschewed unless the obstetrician wishes to advise or instruct her. This is best done immediately after a contraction, before she becomes completely relaxed again.

These periods of amnesic relaxation have two salutary influences upon labor. They ensure complete rest and maximum restitution of the hard-worked muscles, and by inhibiting sympathetic nerve impulses allow full and free circulation within the uterus so that a complete interchange of blood takes place, and the metabolites of muscular effort are not retained. The expulsive power of the uterine and skeletal muscles is thereby enhanced. Inertia or fatigue of a woman or her uterus rarely occur, and the necessity for forceps extraction consequently is minimized.

Careful observation should be made of the emotional changes of the second stage of labor. At first there is a revival of a woman's personality after the transition from the second testing period to the establishment of expulsive contractions. She will express relief and confidence and be alert to her surroundings, asking pertinent questions about the progress and duration of her labor. As the head passes deeply into the birth canal, the onset of amnesia, while relaxing between contractions, will be observed. In mid cavity a careless primitive self may appear. With the onset of a contraction a woman may tersely order her attendant to do this or that. A most docile and cultured person may say in commanding tones "Come on, another one—hurry up, hold my legs." They may give vent to expletives and belchings of no uncer-

desire, during the contractions, a hand to hold; she may need a word of advice or a word of encouragement. This is variable in the different types of women that we have to deal with, but it must be recognized that this is the time above all others when an obstetric attendant should be present with the patient, for once this transition from the first to the second stage has been completed labor becomes a simple and interesting affair.

It is also at this time that a woman should be given an anesthetic should she require it. She should not be allowed to use the apparatus for self-induction. If she is given gas, trichlorethylene or gas and oxygen, the labor is in no way disturbed and there is no necessity to continue the anesthetic once she has assumed the second stage. If she finds the discomfort in her back more than she wishes to tolerate there is no reason why an injection of demerol (pethedin) should not be given, but the large majority of women will recognize that this discomfort is purely transient if they are told of it; they will agree and understand that the backache is not one which will increase, but one which will pass off, as indeed it does.

I frequently say "If, with help, you can put up with this for perhaps a dozen contractions, the backache will go, but I leave it to you to say whether you wish to have anything to relieve the discomfort or not." Most women say "No, it isn't as bad as all that but it feels as though its going to get much worse;" and that is one of the things about labor which must be carefully understood. So many of its sensations are threatening—they feel as if they are going to get very much worse, therefore they wake up in a woman's mind all the associations that she has of labor and all the fear-producing propaganda that has crossed her mind during her young adult life. Strict attention should be given to the breaking down of these fear-producing threatenings of discomfort during labor.

Once the second stage expulsive contractions are established, the woman changes entirely. She enjoys the effort that enables her to take some part; she is more than willing to admit that the passive patience of the first stage had become a great trial to her and now, "thank heavens," they say, "I can do something to help my baby into the world."

The early establishment of expulsive contractions can often be noticed when the woman takes a deep breath as she should when each contraction starts. The expiration will frequently be checkered or halted by a little laryngeal catch. It is quite involuntary, and it is the first indication of the establishment of expulsive contractions. Once that is heard she may be told to hold her breath "at the top" of the next contraction—she will understand from her own sensations what is meant by "at the top of." It is inadvisable to suggest that a woman pushes down or bears down at this stage—there is no advantage to be gained from it and she should be advised to follow the lead of her uterus and to change her routine from relaxation during the contractions as was necessary in the first stage, to relaxation between the contractions which is beneficial in the second stage.

At this time a woman should be told of the rupture of the bag of waters, for a sudden rush of fluid from below may be very alarming if unexpected.

stood. And finally, it remains down and crowns. This early crowning constitutes the *fourth* and final *testing period* of labor. The tightness and stretching is such that women feel they must split, and an instinctive protective resistance may result in an effort to tense the muscles of the outlet.

At this stage the knees should be kept up and not allowed to go down onto the bed again. They should be held at an angle just beyond ninety degrees to the bed, and the left leg held by an assistant. The right foot, if not supported by a second assistant, rests on the left hip of the attendant. The bearing down effort should be stopped. At this time a woman can breathe in and out and not hold her breath, allowing the unaided uterine effort to advance the head without violence. The patient should be kept under firm control, and after two or three contractions the vulval margin loses its sensitiveness, except at the upper quadrant by the clitoric folds. The extending head slowly lifts the occiput above the pubis.

A soft woollen pad should be held in the palm of the right hand to exert gentle pressure on the face and chin to prevent extension of the head before the pubis is well into the nape of the baby's neck. Lifting the chin is a sure way of tearing the perineum and it should be guided upward with the occipito mental line as closely as possible at right angles to the vulval orifice. In this way the smallest diameter of the head passes through the outlet, and many tears and episiotomies are avoided.

The delivery is not painful and the woman is frequently surprised to hear the first grumbling cry of her baby. The arms are freed, usually the posterior first but if an anterior hand presents, by passing the elbow across the infant's chest the arm may be delivered and the pressure on the perineum released. When both arms and shoulders are delivered and the cord is freed, the rotation of the shoulders should be completed by gently turning the child face to pubis while awaiting the next contraction. At this point it is my custom to wipe the baby's face and most mothers like to hold the hand of their child. There is no discomfort but rather elation and excitement. They demand to know its sex but are told that they must wait for the next contraction as its body is not fully born. The child is then delivered slowly and gently by carrying the body upward over the pubis.

After the cord has been separated, the infant is wrapped in a towel and handed immediately to its happy and delighted mother. Her emotional state is now that of pride and achievement—she is transfigured and appears to be a new and different person from the woman who, but a short time previously, labored for her child. As she takes her infant, a hand should be placed on the fundus of the uterus and it will be felt to go into a firm and prolonged contraction which is a manifestation of psychosomatic reaction. After a few minutes the child is placed in a warm cot and the woman is given a drink of hot glucose and water.

The third stage is explained and when the contractions of the uterus become strong enough for her to feel the desire to push down, or when the placenta is in the vagina, she is asked to give a long expulsive effort to squeeze out the spongy afterbirth.

tain quality with neither embarrassment nor apology. Such incidents are not remembered and often cannot be recalled after the child is born. A careless untidiness adds an element of drama which should not be mistaken for distress. But at this time care should be taken to detect the *third testing period* of labor.

When the occiput starts its rotation to the front and commences to exert direct pressure on the pelvic floor, the emotional state of a woman undergoes a sudden and sometimes violent change. It is an important phenomenon that is too frequently overlooked. A feeling of pressure is experienced which is alarming and intense, and the reaction is frequently one of exasperation leading to the expectancy of acute pain. It is the point at which the threat of pain is so real that women demand immediate relief, not for what is but for what they feel is imminent.

A woman obstetrician of wide experience discussed with me during the birth of her child all the phenomena I had recorded and the significance of them to her as a patient. Of this third testing period, she said, "It was the only time during labor that I was actually frightened because, although I was expecting these sensations, I had no idea they would be so intense." Although her sensations may have been intensified by severe injuries at a previous confinement, her observations are of importance.

Warn a woman, immediately this stage is detected in her behavior, that the feeling of pressure or even bursting through the rectum will not materialize. It is a further threat and will pass in two or three contractions. Ask her "Is it painful or does it threaten to be painful?" and advise her not to squeeze her anus up against it but to allow everything to go loose and bulge out below. Remind her that the anesthetic is by her side to use if she wishes. With the restoration of confidence the severity of the sensation speedily diminishes, and the bag of membranes, occiput, or caput succedaneum comes into view. If she is told that the head is visible her effort syndrome is restored and she again exerts herself to expel the child.

The facial expressions and grunts of a woman must not be mistaken for pain. The willingness to take an analgesic is a much better basis for the diagnosis of pain than the outward appearance that accompanies physical exertion and strain. The facial expressions of agony in athletes are not a demand for anesthesia, but evidence of unrestricted determination which, with victory, gives place to the exaltation of successful achievement. I frequently receive letters of complaint from women who have been forced to take an anesthetic by a sympathetic and misguided attendant who has mistaken their facial contortions and grunts for agony and so robbed them, in spite of their remonstrances, of the visible and tangible fruits of victory. A more careful understanding of the phenomena of the late second stage of labor and their true significance would prevent many disappointments and torn perineums, and not a few hurried low forceps deliveries.

As the head comes down on the perineum and the anus is dilated, its advance and retreat should be explained—for, as it slips back, a feeling of frustration and disappointment is experienced if this feature is not under-

trial from beginning to end. Others are conscious only of the changes at the second testing period which is the most constant of all, whereas labors are attended in which all four testing periods present a demand for obstetric skill and understanding. When a phenomenon reoccurs from time to time throughout a series of physiologic labors, its significance should not be overlooked, for it is unlikely that a constantly recurring incident is devoid of importance.

It is obvious that these observations call for a much fuller understanding of the physiologic and chemical changes that occur in normal childbirth. In spite of the clinical advantages, so widely demonstrated by those who teach and practice natural methods, this approach is only in its infancy. When adequate investigation has been made it is likely that a more complete understanding of the normal will enable us to reduce the incidence of abnormality and morbidity in pregnancy, parturition, and puerperium.

TABLE III. COMPLICATIONS OF LABOR

| | GROUP A | GROUP B |
|----------------------------------|---------|---------|
| Fetal distress | 7 | 1 |
| ROL to ROP | 1 | 1 |
| Retained placenta | 1 | 2 |
| POP to brow | 2 | 0 |
| Face to pubes | 1 | 0 |
| Ruptured membranes and med. ind. | 2 | 0 |
| Secondary uterine inertia | 1 | 1 |
| Nipped anterior lip. | 1 | 1 |
| P.P.H. | 1 | 0 |
| Prolapsed arm and posterior | 1 | 0 |
| Disorderly uterine action | 0 | 1 |
| Low transverse arrest. | 0 | 1 |

Column A in Tables I, II, and III gives 100 consecutive cases where women have attended the antenatal classes, and the physiotherapists have had full opportunity of being present throughout labor. All were booked patients.

Column B gives 100 women in the same age groups taken at random from the wards on the same day, where possible, as the delivery of the column A women. All were booked patients. Both columns concern *primiparas* only.

Only those women are included whose labors appeared to be likely to run a normal course when labor started. If labor became complicated later the case has been included.

These women were prepared by, but the labors were *not* conducted by, attendants familiar with the procedures for securing a physiologic childbirth.

Further information for details of the method may be found in the author's books: *Revelation of Childbirth* and *The Birth of a Child*, published in America by Harper and Brothers, New York.

TABLE I. STATISTICS OF 100 CONSECUTIVE DELIVERIES OF WOMEN ATTENDING THE "TRAINING FOR CHILDBIRTH" CLASSES AT A MATERNITY HOSPITAL IN THE MIDLANDS—WITH CONTROLS

| | GROUP A (TRAINING CLASSES) | GROUP B (CONTROLS) |
|---|-------------------------------|-----------------------|
| Average number of hours in labor | 16 hr. 23 min. | 20 hr. 26 min. |
| Average number of attendances at classes* | 7.7 | -- |
| Forceps | 9% | 13% |
| Cesarean section | 0% | 1% |
| Drugs and analgesics | 42% | 98% |
| Analysis of above: | | |
| Minnitts | 5 cases | 76 cases |
| Morphia and Hyocine | 7 doses | 29 doses |
| Mist 3 XVs | 9 doses | 25 doses |
| Heroin | 17 doses | 28 doses |
| Pitocin | 3 doses | 2 doses |
| General anesthetic | 10 cases | 16 cases |
| Nembutal | 6 doses | 6 doses |
| Pethidine | 3 doses | 3 doses |
| Pituitrin | 2 doses | 2 doses |
| Chocolate drops | 1 dose | 2 doses |
| Seconal | 2 doses | 1 dose |
| Chloral hydrate | 1 dose | 1 dose |
| Syrup of chloral | 1 dose | 3 doses |

N. B. Drugs were never withheld in this GROUP A.

*Thirty-one cases attended over 10 times. The average time in labor for these is thirteen hours, forty-six minutes. It would therefore seem that there might be a case here for a *minimum* number of attendances (say 10) when arranging classes. The ideal is, of course, a weekly attendance throughout pregnancy.

TABLE II. COMPLICATIONS OF PREGNANCY

| | GROUP A | GROUP B |
|-------------------------------------|---------|---------------|
| Breech extraction and version 35/52 | 4 | 2 |
| Monila vaginitis | 1 | 0 |
| Overdue—medical induction | 10 | 15 |
| E.U.A.—high head | 2 | 4 |
| Pre-eclampsia | 5 | 5 |
| A.P.H. | 4 | 2 |
| Hydramnios | 1 | 0 |
| Punctured membranes | 2 | 9 |
| Removal fibroid | 1 | 0 |
| Undiagnosed twins | 1 | (diagnosed) 1 |
| Mitral stenosis | 0 | 4 |
| Chronic nephritis | 0 | 1 |
| Pleurisy and bronchitis | 0 | 2 |
| Anemia and hypertension | 0 | 1 |

Such labors can be seen in the majority of healthy well-conducted women. There is rarely any hemorrhage, and seldom more than four to five ounces. Obstetric shock is not seen and lacerations are unusual. The well-being and happiness of the mother is impressive and the lusty health of the infant gratifying, for the major anxieties of labor are in the third stage and from these, in this way, the obstetrician may be protected.

It should be understood that no two labors are alike. They vary as widely as the natures of women. They are influenced by association, environment, and teaching. The experience and ability of the attendant is an important factor, for upon that the confidence and self-control of the woman depends to a large extent.

The four testing periods of labor vary in the intensity of their manifestation. Many women may give birth to a child without displaying a phase of

of cases was designated as the prophylactic group. Twenty of the thirty patients were alive five years after first being seen, giving an absolute cure rate of 66.6 per cent. The remaining 133 patients were termed recurrent cases. They included many inoperable patients with fixed uteri and large abdominal masses. There were also recurrences in the vaginal vault and about the hymeneal ring and urethra. And finally, there was carcinoma of the cervical stump. There were 33 five-year cures in this group, giving an absolute cure rate of 24.8 per cent. The prognosis is determined by the gross extent of the disease and by the histologic type of carcinoma. The gross extent of the disease with its prognostic significance is as follows: dividing the five-year end results into five specified groups. Group 1, uterus not enlarged, 66 per cent salvage; Group 2 a, uterus not enlarged greater than a 2½-month gestation, 37.9 per cent; Group 3 a, carcinoma extending to the cervix, 24.3 per cent; and Group 3 b, carcinoma beyond the uterus, 11.2 per cent salvage. The tumors were also divided into histologic types for the purpose of prognosis, grades 1 and 2 giving a 47.2 per cent salvage, grades 3 and 4 giving a 22.8 per cent salvage and adenoacanthoma giving a 51.3 per cent salvage. No true evaluation of the difference between operative and radiation therapy could be made because of the fact that there were more cases in the radiation group and, in the main, these also were the more severely ill. Neither could the question of cure rate from hysterectomy with or without radiation be solved.

L. M. HELLMAN.

Buschke, Franz, and Cantril, Simeon T.: Treatment of Carcinoma of the Uterine Cervix, West. J. Surg. 55: 152, 1947.

The evolution of radiation therapy in the treatment of carcinoma of the cervix is reviewed. The basic principles of treatment used by the author are those of the Curie Institute originally described by Regaud and his co-workers. The vaginal applicators used for treatment are those developed at the Holt Radium Institute in Manchester, England. Minute attention is given to the details of anatomic distribution of the radium. In all cases, except Stage 1, the radium is followed by roentgen therapy. Rectal and bladder complications are more frequent if roentgen therapy precedes the radium therapy.

The results of treatment are as follows, based on the five-year cure rate:

Stage 1—83%
Stage 2—56%
Stage 3—38%

WILLIAM BICKERS.

Halberstaedter, L., and Hochman, A.: The Artificial Menopause and Cancer of the Breast, J. A. M. A. 131: 810, 1946.

The authors review extensively the literature of artificial menopause in cancer of the breast both in human beings and in experimental animals. The authors treated 60 women suffering from cancer of the breast and its metastases by producing artificial menopause with x-radiation of the ovaries. Thirty-four women, or 56 per cent, benefited from this treatment. The improvement due to the interruption of estrogenic secretion is of short duration, since vicarious estrogenic secretion from other sources than the ovaries intervenes. Typical adenocarcinomas are more susceptible than anaplastic cancer of the breast due to the estrogen-inhibiting influence of the artificial menopause.

WILLIAM BERMAN.

Black, B. Marden, and Howe, Rulon F.: Primary Carcinomas of the Breasts, Uterus and Colon, Proc. Staff Meet. Mayo Clin. 21: 484, 1946.

Multiple primary malignant lesions have been found most frequently at autopsy, and their differentiation from recurrent or metastatic malignant lesions has been based on pathological rather than on clinical findings. The clinical diagnosis of multiple primary malignant lesions has been more difficult to establish.

In the case reported the patient was first seen at the Mayo Clinic in July, 1939; she came to the hospital within a few days after her physician had discovered a small nodule

Department of Reviews and Abstracts

Selected Abstracts

Malignancies

Graham, M.: The Effect of Radiation on Vaginal Cells in Cervical Carcinoma. I. Description of Cellular Changes. II. The Prognostic Significance, Surg., Gynec. & Obst. 84: 166, 1947.

Two extremely significant papers are presented which discuss the effect of radiation therapy on vaginal cells as shown by the vaginal smear technique and the prognostic significance of this change in carcinoma of the cervix. In the first paper 206 cases of cervical carcinoma treated by radiation therapy were studied by this method. The changes seen in the cells were comparable in every respect to the irradiation changes seen in cervical biopsy in similar types of patients. The pyknosis and degeneration of nuclei, the swelling and vacuolization of cytoplasm, the evidence of abnormal mitoses and leucocytic infiltration with the formation of giant cells, are all seen in vaginal secretion just as they appear in cervical biopsies. The author points out that the vaginal smear method is a much simpler way of studying the reaction of both tumor and normal cells. It is often difficult to do serial biopsies on treated patients.

The second paper concerns the prognostic significance of these changes in 73 instances of cervical carcinoma. It is pointed out that there are two types of response as seen by the vaginal smear method. The good response shows a rather rapid disappearance of malignant cells and an equally rapid appearance of radiation change in the normal cells of the vaginal secretion. The poor response on the other hand shows neither a disappearance of malignant cells nor any marked radiation change in the normal cells. In the 73 cases studied, divisions into two groups, i.e., good and poor response to radiation, gave a prognostic accuracy of 88 per cent. While the follow-up of these cases is admittedly short and the series extremely small, nevertheless earlier work on cervical biopsy would seem to substantiate the claims made in this paper. If the method holds good after further study and longer follow-up, then it will give an excellent means for early prognosis as to the effect or lack of effect of radiation therapy.

L. M. HELLMAN.

Taylor, Howard C., Jr., and Becker, Walter F.: Carcinoma of the Corpus Uteri, Surg., Gynec. & Obst. 84: 129, 1947.

This paper contains a review of 531 histologically verified cases of carcinoma of the body of the uterus which were admitted to Memorial Hospital during the period 1926 to 1940, inclusive. The total five-year cure rate was 38 per cent. There were 386 primary cases of which 39.9 per cent were alive and well in five years. If the patients who were lost track of when free from cancer, and those dying of intercurrent disease unrelated to carcinoma were subtracted, the five-year cure rate was approximately 45 per cent. There were 163 patients who received prior treatment for carcinoma of the body of the uterus, who were admitted to the Memorial Hospital during the fifteen years under consideration. Thirty of these patients presented no clinical evidence of carcinoma, and the diagnosis was confirmed only by reviewing the microscopic material from the institution in which they were originally treated. This group

Mm. Masse, Traissac and Dax: Treatment of Endometriosis of the Rectovaginal Septum by Implantation of Testosterone Pellets, *Compt. rend. Soc. Franc. de Gynec.* 26: 105, 1946.

The authors, discouraged by necessity of frequent injections of testosterone propionate necessary to control the pain of endometriosis, decided to implant pellets of this drug to overcome this problem. In two cases the authors implanted such pellets; 200 mg. and 300 mg. in the respective instances.

In the first case, a woman, aged 40 years, gave a history of menorrhagia, polymenorrhea, severe dysmenorrhea associated with perineal radiating pains. Clinically there were present two nodules the size of small hazelnuts with smaller areas of endometriosis of the cul-de-sac and rectovaginal septum. Intramuscular injections of testosterone, 100 mg. per month, gave but minimal relief of pain. In February, 1946, a 200 mg. pellet was implanted. The effect was immediate, menses became regular, perineal pain disappeared, and, while the nodulation of the involved areas could be felt, they were no longer painful.

The second case was a 44-year-old woman submitting a history of dysmenorrhea of increasing severity and associated for six months with rectal tenesmus. A chocolate cyst was removed through laparotomy at which time rather rectovaginal endometriosis was discovered. Ten days later a 300 mg. testosterone propionate pellet was implanted. Since that time the menses recurred regularly and without pain.

C. E. FOLSOME.

Gynecology

Arostegui, Gonzalo E., and Blanco, F. Leon: Brenner Cell Tumors of the Ovary: A Literature Review and Presentation of Three Cases, *Rev. cubana de obst. y ginec.* 7: 27, 1945.

The authors review the literature on the topic of Brenner cell tumors of the ovary as evaluated from 84 references. They add three new cases of their own to the medical writings. Their patients were aged 33, 34, and 60 years, respectively. In all instances the tumors in their series were unilateral and localized in each case in the right ovary. Grossly the tumors varied in size, viz.: (1) 4 by 3 by 2 cm., (2) 12 by 10 by 5 cm., and (3) 5 cm. in diameter. Histologically, they were all classed as Brenner cell tumors of Meyer's Group A.

C. E. FOLSOME.

Shaw, H. N., and Gaspar, John: Chronic Salpingitis, *West. J. Surg.* 55: 81, 1947.

An attempt is made to evaluate sulfonamide therapy in the treatment of acute pelvic inflammatory disease. It could not be demonstrated that resolution of the inflammatory process proceeded more rapidly when sulfonamides were added to the usual supportive treatment. Management of this condition at the Los Angeles County General Hospital now is limited to bed rest, adequate diet and the sulfonamides only in very acute cases without pelvic masses. The white blood cell count and sedimentation rate are held to be rather accurate indices of the degree of inflammatory activity.

The presence of inflammatory masses persisting after adequate conservative treatment is considered an indication for operation. Deep cautery of the cervix always precedes operation and, where the inflammatory process is extensive, the removal of both tubes, both ovaries, and the uterus is indicated. In cases where purulent material is spilled, 5 to 8 Gm. of sulfonimide crystals are left in the peritoneal cavity. The appendix should be removed as routine.

There were 11 deaths in these 759 patients who comprised this study. Two of these deaths resulted from advanced pelvic tuberculosis. Seven patients died of peritonitis with or without obstruction. One patient died from peritonitis originating in a cervical stump abscess. Perhaps she could have been saved with proper drainage.

WILLIAM BICKERS.

in the right breast. A radical mastectomy was done and the tumor was found to be an adenocarcinoma grade 2; there was no involvement of the regional lymph nodes, but post-operative roentgen therapy was employed. Two years later, in June, 1941, a small tumor was found in the left breast on routine examination. In the area of the radical mastectomy on the right side there was no evidence of local or regional recurrence. A left radical mastectomy was done; the tumor was found to be an adenocarcinoma, grade 4, with no evidence of lymph node involvement. The patient was in good health until May, 1943, when her menstrual flow increased in amount; and in the next six months the menorrhagia became continuous, so that in November, 1943, a total hysterectomy was done at another hospital. An adenocarcinoma, grade 1, of the fundus of the uterus was found. This diagnosis was confirmed by examinations of sections of the malignant tissue at the Clinic. The patient was again admitted to the Clinic in October, 1945. For a year she had noted a mass in the right quadrant of the abdomen, and in the last few months had had cramping abdominal pains and constipation, with considerable loss of weight. A diagnosis of carcinoma of the ascending colon was made on x-ray examination. Radical resection with a side-to-side ileocolostomy was done. The tumor was found to be an adenocarcinoma, grade 2, which had involved the regional lymph nodes. The carcinomas in this case fulfilled Goetze's criteria for multiple primary malignant lesions.

The authors suggest that with earlier recognition and improved treatment of carcinoma of various types, more patients will survive the treatment of one neoplasm for long periods and that it seems probable that a larger number of cases of multiple primary carcinoma will be recognized. The necessity for the careful follow-up of cancer patients is evident.

HARVEY B. MATTHEWS.

Endocrinology

Brетеche, M.: Hypothyroidal Cervicitis, *Compt. rend. Soc. Franc. de Gynec.* 26: 114, 1946.

Brетеche, in his study of a case of one-child sterility, in a 25-year-old woman, observed a correlation of hypothyroid state and refractive cervicitis resistant to local therapy. Repeated coagulations of the cervix, sulfonamides, and other therapy failed to clear up this condition. However, because of a nodular goiter and a gradually developing hyperthyroid state with cardiac and ocular symptoms, the basal metabolism rate changing from -11 to a +18, a hemithyroidectomy was done. The basal metabolism rates then fluctuated from a -25 to -59 per cent, necessitating thyroid extract. As long as the thyroid was administered the cervicitis and "erosion" disappeared. A reduction of the thyroid reproduced cervical symptoms. Incidentally, the patient became pregnant twice, delivering two normal children.

Because of the above cases the writer reviewed 263 cervicitis cases. He found that 226 (86 per cent) of these cases were upon an infectious basis; that 21 cases, or 8 per cent, were indisputably upon the basis of hypothyroidism, while the remaining 16 cases, 6 per cent, may possibly have been associated with deficiency in thyroid function.

C. E. FOLSOME.

Endometriosis

Teilum, Gunnar: Carcinoma Arising in Ovarian Endometriosis, *Acta obst. et gynec. Scandinav.* 25: 377, 1945.

Teilum reports a case of adenocarcinoma in the ovary of a 42-year-old woman, with histologically reliable and demonstrable *anlage* suggesting certainty of origin, in his opinion, from the mucosa of a typical chocolate cyst. Upon the inner wall of the cyst were found multicentrically developed papillomatous tumor tissue ingrowing into the cyst wall. In other areas he was able to demonstrate a transition from the normal endometrial epithelium to tumor. Endometriosis, without malignancy, was demonstrable in the opposite ovary. The uterus exhibited slight polypoid hyperplasia of the endometrium.

C. E. FOLSOME.

The authors consider abortion their most burning and social problem. Fifty-seven per cent of the deaths were in women under 30 years of age, and, more important, the writers estimate that associated inflammatory disease causes illness, invalidism, or sterility in over 10,000 cases yearly. While the sequelae can be treated, the causes are social and possibly legal. The causes should be considered as diseases of the nation.

Deaths in childbirth have reduced steadily since 1751; in the years 1936 to 1943 the rate was 0.29 per cent. In Helsinki University Hospital the direct deaths of childbirth were 0.28 per cent (19,965 births, 48 deaths)—divided as follows: 84.4 per cent of deaths were from country districts, 15.6 per cent were urban origin, and 13.0 per cent were unmarried. Only 32.4 per cent of the maternity cases could be admitted to the hospital because of lack of bed space.

The major causes of obstetric death in Finland include 461 cases of toxemias of pregnancy; 595 cases of puerperal sepsis; 199 other hemorrhages; 93 morbid states; 129 puerperal emboli; 78 placenta previa; 68 dystocia; and 49 cases of ruptured uteri. Septicemia has entirely disappeared from the hospital series after 1941, but toxemias are increasing in frequency.

In the hospital series (19,965 births and 48 deaths) cesarean section death rate was 5.4 per cent (31.0 per cent eclampsia mortality), while 46.0 per cent of cesarean deaths were attributed to heart failure.

The authors conclude that the most important means of decreasing childbirth mortality is prophylaxis. The text is illustrated by 13 well documented tables. C. E. FOLSOME.

Beclere, Claude, and Simonnet, H.: *Postpartum Amenorrhea Due to Secondary Hypophyseal Insufficiency and Its Treatment*, *Presse méd.* 12: 175-177, 1946.

The authors have described in previous articles two principal types of amenorrhea, the hypohormonal and the hyperhormonal. A third type, that which occurs post partum, is now discussed on the basis of their experience with eighteen cases treated by the administration of gonadotrophins. Three of these patients had experienced amenorrhea for twelve, nine, and eight years, respectively. The physical examinations of these eighteen patients revealed atrophy of the uterus in each case. The history in fourteen of the eighteen patients revealed previous menstrual irregularities, late onset of the menses, previous episodes of amenorrhea, and variations from normal in amount and interval.

Laboratory examinations revealed gonadotrophins present in amounts less than 10 mouse units and estrogens present in amounts less than 100 international units which the authors state would indicate primarily a hypophyseal insufficiency and secondarily an ovarian failure. This secondary hypophyseal failure has an abrupt onset as a result of the pregnancy. The authors state that the evidence points to increase in function of the hypophysis early in pregnancy and diminishing function in the end of pregnancy. The enormous hormonal production by the placenta probably inhibits the gonadotropic secretion by the hypophysis. It was felt that the levels of gonadotrophins and the absence of vasomotor waves excluded menopause praecox as a cause of amenorrhea in these cases of postpartum amenorrhea.

The eighteen cases were treated by injection of gonadotrophins alone with success in fifteen cases. One other patient was given estrogens and progesterone in addition and menstruation occurred. In only two cases was treatment unsuccessful. The authors state that postpartum amenorrhea of the type herein described is the instance of hypophyseal insufficiency where gonadotrophins alone are indicated. L. M. RANDALL.

Miscellaneous

Lubinski, H. H., and Portnuff, J. C.: *The Influence of Heat and Formalin Upon the Rh Agglutinin*, *J. Lab. & Clin. Med.* 32: 178, 1947.

A differential sensitivity of agglutinogens to heat and formalin is demonstrated. The authors have shown that heating destroys the reactivity of Rh agglutinin to both anti-Rh

Gynecologic Operations

Sardina, M. C. D., and Revilla y Aguda, J. M.: Cervicocervical Fistula, *Rev. cubana de obst. y ginec.* 7: 55, 1945.

The authors report an unusual case of cervicocervical fistula occurring in a 42-year-old patient. The patient had suffered a rectovaginal fistula following her first pregnancy delivered by forceps. Fifteen months later she experienced an incomplete abortion requiring a curettage to remove incomplete products of conception. An incidental appendectomy was done fifteen days later. For the next seventeen years the patient was troubled with leucorrhea, later on with menorrhagia and severe secondary dysmenorrhea. The later symptoms indicated a panhysterectomy, which was done. Preoperative hysterosalpingography had demonstrated the rare fistula tract which was confirmed upon operation. Final pathologic diagnosis was chronic cervicitis with posttraumatic cervicocervical fistula.

C. E. FOLSOME.

Labor

Dennen, Edward H.: The Selection of an Obstetric Forceps to Suit the Case, *Virginia M. Monthly* 150: April, 1947.

The author advocates the use of a large variety of forceps for particular obstetrical indications. For occiput anterior position on the perineum many types of instrument will satisfy the requirements. With a low pubic arch he prefers a forceps with a good pelvic curve. The Simpson, Elliott, or Tucker-McLane instruments are recommended. For occiput anterior above the pelvic outlet a fixed axis traction forcep is preferred. In the posterior occiput, Kielland forceps are preferred to the Scanzoni maneuver. The only exception is in the anthropoid pelvis where rotation is difficult and here delivery as a posterior occiput is preferred. For aftercoming heads in breech extractions the Piper forceps finds an important place. A high transverse head with posterior parietal presentation requires the Barton forceps.

WILLIAM BICKERS.

Paruianen, Sakari, and Pärnänen: Obstetrical and Puerperal Diseases Causing Mortality in Finland, *Acta obst. et gynec. Scandinav.* 26: 1-72, 1946.

The authors, from the First and Third Women's Clinic, Helsinki, review statistical maternal mortality data obtained from the Central Statistical Office of Finland and compare it to these findings of the mortality records in their clinics. There were 185,363 deaths in Finland during the years 1936 to 1943, inclusive, and in this period 2,562 women died of diseases of pregnancy, childbirth, or the puerperal state, an incidence of 1.39 per cent. In the same period were 593,250 pregnancies and 1,727 deaths in childbirth, a ratio of 345 births to each maternal death.

At the two clinics mentioned above, 221 women died of obstetric or puerperal causes during the years 1935 to 1944.

The death rate in diseases of pregnancy, childbirth, and the puerperal state was on an average 1.39 per cent of the total death rate of women in Finland, 6.35 per cent of the death rate of 15- to 49-year-old women, and 10.1 per cent of the death rate of 30- to 34-year-old women. The mortality rate is steadily decreasing. While 79.7 per cent of the total population live in the country, 73.1 per cent of deaths were from rural districts. Twenty-three per cent of the deaths were single women, 66.6 per cent died in hospitals, 12.9 per cent died under treatment at home, and 20.5 per cent were not treated.

Abortions accounted for 28.9 per cent of the maternal deaths. In these abortion cases 93.0 per cent were septic and criminal, with 48.6 per cent occurring among the town population, and 52.7 per cent among the unwed mothers. The hospital abortion death rate was 3.1 per cent (5,113 abortions, 159 deaths). There has been a rapid increase in the number of abortions, being seven times greater in the hospital series. It is calculated that about 300,000 abortions took place in Finland between 1936 and 1943.

signs of tumor cells on the slides. In cancer of the endometrium the diagnosis is somewhat more difficult. The error of correct diagnosis is about 2 per cent. A number of cases of diagnosis of cancer by vaginal smear are quoted.

WILLIAM BERMAN.

Newborn

Bush, J. A. Kyle, Lenox, Cora C., and Myers, Hu C.: Volvulus Neonatorum, South. Surgeon 13: 204, 1947.

Volvulus neonatorum is caused by certain factors resulting from abnormal embryologic development. Incomplete rotation upon the superior mesenteric artery or failure in the complete degeneration of the yolk stalk may produce anatomical changes contributing to the development of volvulus. A case is reported in the newborn; the infant was seen six days after birth at which time persistent vomiting had resulted in dehydration and icterus. X-ray examination revealed obstruction in the duodenum. The infant was treated by a nasal tube and injections of fluids, and operated upon on the tenth day of life. The mesentery was found rotated through one complete circle with resulting obstruction at numerous points in the small intestine. Obstruction was relieved by uncoiling the intestine and placing the mesentery in proper relation to it. The patient recovered.

WILLIAM BICKERS.

Weymuller, Charles A., Beck, Alfred C., and Ittner, Elizabeth J.: Measures for the Protection of Newborn Infants, J. A. M. A. 133: 78, 1947.

The authors mention three circumstances that favor the common type of nursery infections.

1. Unnecessary contact with visitors, nurses and physicians.
2. Inadequate isolation of the infants from one another in the nursery.
3. Faulty technique for preventing the spread of contamination.

Certain corrective changes in the visiting hours, nursing and doctors' technique in the handling of babies, and the supervision of ward maids and cleaning women are made. Every nursery unit has its own complete examining room. The architecture of the nurseries is such as to prevent crowding. Nursing assignments are such as to permit one nurse to care for eight babies and one premature only. She has complete care of those babies. The formula room is completely removed from the hospital section containing the nurseries and sick patients.

Nurses are carefully supervised and inspected and are relieved of duty immediately when ill. Their throats are cultured when they start on duty and whenever it is indicated while on duty. Numerous other precautionary measures in the nurseries are mentioned.

The authors report excellent results in their prophylactic anointment of newborn infants with 15 Gm. of 5 per cent sulfathiazole ointment. As a result of the war and nursing shortage an epidemic of diarrhea occurred in October, 1945, and affected 19 infants. All of them recovered.

WILLIAM BERMAN.

and anti-Rh blocking sera, while the A, B, M, and N agglutinogens do not lose their reactivity to their respective anti-sera under similar conditions. Treatment with formalin evokes a similar differential response, but to a lesser degree.

The authors mention variation in location in the cell, chemical structure, or quantitative differences as possible explanations for these observed phenomena. S. B. GUSBERG.

Sperling, Gladys A., Loosli, J. K., Barnes, L. L., and McCay, Clive M.: The Effect of Coffee, Human Diets, and Inheritance Upon the Life Span of Rats, *J. Gerontology* 1: 426, 1946.

Three diets were fed to groups of eighty rats throughout life. One diet resembled that eaten by many persons in northeastern United States. A second diet was similar to this but supposedly better because of the inclusion of more whole wheat bread, milk, and liver. A third was supplemented with vitamins. Each diet was fed with and without a moderate supplement of coffee, equal to about a cup per person per day. Life span data afforded no evidence for the superiority of any of the three diets. Coffee at this low level was not injurious and may have had a favorable effect upon the survival of the females. An auxiliary study in which coffee was fed as the sole source of fluid during lactation and the growth of three generations afforded additional evidence that even large amounts exerted no unfavorable effect. Evidence is presented that inheritance exerts a definite influence upon the length of life of the white rat. EDWARD C. HUGHES.

Davenport, J. W., Jr.: The Prevention of Rh Isoimmunization Due to Blood Transfusion, *New Orleans M. & S. J.* 99: 376, 1947.

The prevention of Rh isoimmunization is a responsibility which the medical profession must assume and this is particularly true as regards the female. Of the total female population, 15 per cent are Rh negative. The transfusion of these females with Rh-positive blood will result in immunization in approximately one-half of them. It is imperative that routine typing include little girls and infants who are to be transfused. Transfusion of these individuals with Rh-positive blood will immunize many of them to the point where in subsequent marriage to an Rh-positive male they will be subjected to the possibility of giving birth to erythroblastotic infants. Since there is no way of de-immunizing an Rh-negative female already immunized by Rh-positive transfusions, her reproductive potential is nil.

Regarding male patients, the problem arises only in relationship to multiple transfusions. WILLIAM BICKERS.

Meigs, Joe V.: The Vaginal Smear, *J. A. M. A.* 133: 75, 1947.

The author reports 2,749 cases of vaginal smear with an error of only 3.3 per cent. It is obvious that this method is of extreme value in enabling the physician, if not to make a definite diagnosis, at least to screen satisfactorily women who come for routine examination. A positive smear indicates that careful further studies both by smear and by biopsy are indicated. The author has rarely allowed a positive vaginal smear to be the sole reason for radical surgery. The individual cell is the most important feature of the vaginal smear technique. The nucleus of the cell is the main diagnostic criterion. The cancer cell has a large abnormal nucleus and in groups a variation in size and shape is obvious. It is important to note the paucity of cytoplasm as compared to the amount seen in the normal cell. The ratio of nucleus to cytoplasm is different in the cancer cell from that in the normal cell. In cancer of the endometrium the same criteria are true, but there is less variation in the size and shape of the nucleus, yet the difference is real after cytological criteria for diagnosis are given.

It is difficult to explain the finding of a positive smear and a negative biopsy. The number of errors of false positive smears has been 2 per cent. In 3.5 per cent of the cases of cervical cancer in which the slides were called negative, reobservation still did not show

It is the opinion of the writer that the wide variety of ages which the patient gave in recording the births of previous children, and particularly her rapid "aging" in the last few of these birth certificates mitigates against the acceptance of her stated age. The fact that the earliest birth certificate we are able to obtain records six previous children born to this mother instead of 14, the number she states were born prior to coming to this community, also casts doubt on her story. It is not felt, on the basis of the investigation to date, that this can be accepted as a delivery at an advanced age.

JOHN H. HOLZAEFFEL, M.D.

COLUMBUS, OHIO

July 22, 1947.

Item

American Board of Obstetrics and Gynecology, Inc.

Examinations

The next written examination (Part I) for all candidates will be held in various cities of the United States and Canada on Friday, Feb. 6, 1948, at 2:00 P.M. Candidates who successfully complete the Part I examination proceed automatically to the Part II examination held later in the year.

A number of changes in Board regulations and requirements were put into effect at the last annual meeting of the Board held in Pittsburgh, Pa., from June 1 to June 7, 1947. Among these is the new ruling that the Board does not subscribe to any hospital or medical school rule that certification is to be required for medical appointments in ranks lower than Chief or Senior Staff of hospitals, or Associate Professorship in Schools of Medicine, for the obvious reason that such appointments constitute desirable specialist training. At this meeting the Board also ruled that credit for graduate courses in the basic sciences which involve laboratory and didactic teaching rather than clinical experience or opportunities will be given credit for the time spent up to a maximum period of not more than six months regardless of the duration of the course.

Applications are now being received for the 1948 examinations. Closing date for these applications will be Nov. 1, 1947.

For further information and application blanks address Paul Titus, M.D., Secretary, 1015 Highland Building, Pittsburgh 6, Pennsylvania.

PAUL TITUS, M.D.

Correspondence

Advanced Age for Childbirth

To the Editor.—The birth of the twenty-seventh child to a 65-year-old Negro woman was publicized both in the lay press, September, 1946, and in the *Journal of the American Medical Association*. This publicity has resulted in many inquiries to this clinic for verification. The present letter summarizes the case as well as the efforts made to establish the patient's true age.

The patient, Mrs. M. J., entered the Prenatal Clinic of the Ohio State University Hospital in July, 1946. She purported to be gravida xxi, para xxvi, and stated that she was 65 years of age. Her last menstrual period was March 22, 1946, but she gave a history of menses the first few months of each previous pregnancy. Menses had started at the age of 13 years, the patient had a 28-day cycle and flowed three to five days with no unusual blood loss with her periods. Fetal movement was first noticed April 5, 1946.

Physical examination revealed an obese Negro woman; weight 284 pounds; height 5 feet 2¾ inches. Patient did not appear to be her stated age of 65 years, but looked to be approximately 45 years of age. No fetal heart was heard; Chadwick's and Hegar's sign were positive; ballotment was present. Pelvimetry indicated a gynoid pelvis. X-ray report: single fetus, cephalic presentation, adequate pelvis. The remainder of the prenatal course was uneventful, and a living female was delivered spontaneously, Sept. 26, 1946.

A review of the patient's obstetric history reveals that she had six sets of twins and 15 single children. She had been married twice. Her first husband was killed in a mine accident in Greensboro, N. C., in 1913. The second husband is a resident of this city and is 60 years of age.

Verification of an individual's age is not always easy. This patient's claim rests chiefly upon her birth date as recorded in her family Bible. The date of birth is given as April 5, 1881, and her maiden name is recorded as Mary Matilda Walker. A photostatic copy of this Bible record was obtained in the course of efforts to establish her actual age.

The patient referred the writer to a white family of this city with whom she had had long contact. The oldest living member of this family, an insurance agent, aged 35 years, was willing to sign a certified statement to the effect that the patient had worked as a cook for his grandfather in Hickory, N. C. This man further stated that to the best of his memory the patient's present professed age coincides with that she gave when she was in his grandfather's employ. An attempt to verify the marriage and subsequent death of the first husband was unsuccessful. The Recorder of Deeds in Greensboro, N. C., reported that no vital statistics were kept in North Carolina before 1913.

A systematic review of the birth certificates of the patient's children, however, revealed a marked discrepancy. In March, 1927, the patient delivered twins whose births are recorded at the Bureau of Vital Statistics. On these birth certificates the mother's age is given as 27, which would make her age, at present, 48. It is then noted that the ages for the mother in subsequent births are not chronologic. In 1928, her age was given as 43; in 1930, 44; in 1936, 55; and in 1942, 61. Scrutiny of the initial birth certificate on file in Columbus, Ohio, shows that this patient then (in 1927) reported six previous children. It would seem, therefore, that this patient had six children by her first marriage rather than the purported 14.

- San Francisco Gynecological Society.** (1929) *President*, Albert M. Vollmer. *Secretary*, Daniel G. Morton, University of California Hospital, San Francisco, Calif. Regular meetings held second Friday in month from October to April, University Club, San Francisco, or Claremont Country Club, Oakland, Calif.
- Texas Association of Obstetricians and Gynecologists.** (1930) *President*, T. F. Bunkley. *Secretary*, J. McIver, 714 Medical Arts Bldg., Dallas, Tex.
- Michigan Society of Obstetricians and Gynecologists.** (1924) (Formerly the Detroit Obstetrical and Gynecological Society.) *President*, Clarence E. Toshach. *Secretary*, John P. Ottaway, 1551 Woodward Ave., Detroit, Mich. Meetings first Tuesday of each month from October to May (inclusive).
- Central New York Association of Obstetricians and Gynecologists.** (1938) *President*, Raymond J. Pieri. *Secretary*, Nathan N. Cohen, 713 E. Genesee St., Syracuse, N. Y. Meets second Tuesday of September, November, January, March, and May.
- Alabama Association of Obstetricians and Gynecologists.** *President*, Gilbert F. Douglas. *Secretary*, Hunter Brown, 1922 South Tenth Ave., Birmingham, Ala.
- San Antonio Obstetric Society.** *President*, I. T. Cutter. *Secretary*, S. Foster Moore, Jr., San Antonio, Tex. Meetings held first Tuesday of each month at Gunter Hotel.
- Seattle Gynecological Society.** (1941) *President*, Carl M. Helwig. *Secretary*, Roger E. Stewart, Stimson Bldg., Seattle, Wash. Meetings held on third Wednesday of each month.
- Denver Obstetrical and Gynecological Society.** (1942) *Secretary*, Emmett A. Mechler, 1612 Tremont St., Denver, Colo.
- Wisconsin Society of Obstetrics and Gynecology.** (1940) *President*, J. M. Freeman. *Secretary-Treasurer*, Lionel T. Servis, 425 East Wisconsin Ave., Milwaukee. Meetings held in May and October.
- San Diego Gynecological Society.** (1937) *President*, R. C. Hall. *Secretary*, D. Dalton Deeds, 2001 Fourth Ave., San Diego, Calif. Meetings held on the last Wednesday of each month.
- North Dakota Society of Obstetrics and Gynecology.** (1938) *President*, Ralph E. Leigh, Grand Forks. *Secretary*, G. Wilson Hunter, 807 Broadway, Fargo, N. D.
- Virginia Obstetrical and Gynecological Society.** (1936) *President*, S. E. Oglesby. *Secretary*, L. L. Shamburger, 628 State Office Bldg., Richmond 19, Va. Next meeting not announced.
- Columbus Obstetrical and Gynecological Society.** (1944) *President*, Wynne M. Silbernagel. *Secretary*, Zeph J. R. Hollenbeck, 9 Buttles Ave., Columbus, Ohio. Meetings held fourth Wednesday of each month.
- Naussau Obstetrical Society.** (1944) *President*, Austin B. Johnson. *Secretary*, Robert S. Millen, Westbury, N. Y. Meetings, bimonthly from October to May.
- Bronx Gynecological and Obstetrical Society.** (1924) *President*, George Muscillo. *Secretary*, Milton D. Klein, 1882 Grand Concourse, New York 57, N. Y. Meetings, fourth Monday monthly from October to May.
- Washington State Obstetrical Society.** (1936) *President*, John H. Fiorino, Everett. *Secretary*, H. H. Skinner, Yakima, Meetings, first Saturday of April and October.
- Kansas City Obstetrical and Gynecological Society.** (1922) *President*, Thomas J. Sims. *Secretary*, LeRoy Goodman, 702 Bryant Bldg., Kansas City, Mo. Meetings, last Thursday, September, November, January, and March; first Thursday, May, University Club.
- Los Angeles Obstetrical and Gynecological Society.** (1914) *President*, Carl E. Krugmeier. *Secretary-Treasurer*, A. M. McCausland, 3780 Wilshire Blvd., Los Angeles, Calif.
- North Carolina Obstetrical and Gynecological Society.** (1932) *President*, Wallace B. Bradford. *Secretary*, Richard B. Dunn. Meetings semiannually.
- The Society of Obstetricians and Gynecologists of Canada.** (1944) *President*, William A. Scott. *Secretary*, James Goodwin, 516 Medical Arts Bldg., Toronto, 5. Meetings held annually, date of next meeting to be announced later.
- Akron Obstetrical and Gynecological Society.** (1946) *President*, L. L. Bottsford. *Secretary-Treasurer*, N. E. Wentsler, 1029 Second National Bldg., Akron 8, Ohio.
- Minnesota Society of Obstetrics and Gynecology.** *President*, L. M. Randall. *Secretary*, Russell J. Moe, 205 West Second St., Duluth, Minn. Meetings held spring and fall.
- Miami Obstetrical and Gynecological Society.** (1946) *President*, M. C. Wilson. *Secretary*, George A. Mitchell, Huntington Bldg. Meetings, second Thursday in January, March, May, and November.
- Omaha Obstetrical and Gynecological Society.** (1947) *President*, M. E. Grier. *Secretary*, B. V. Reaney, 1116 Medical Arts Bldg., Omaha 2, Neb. Meetings held third Wednesday in January, March, May, September, November.
- Oklahoma City Obstetrical and Gynecological Society.** (1940) *President*, Le Roy H. Sadler. *Secretary-Treasurer*, John W. Records, 301 Northwest 12 Street, Oklahoma City.
- Cleveland Obstetrical and Gynecological Society.** (1947) *President*, Robert E. Faulkner. *Secretary*, G. Keith Folger, 10515 Carnegie Ave. Meetings on fourth Tuesday of September, November, January, March, and May at University Club, 3813 Euclid Ave., Cleveland 15, Ohio.

ROSTER OF AMERICAN OBSTETRICAL AND GYNECOLOGICAL SOCIETIES*

(Appears in January, April, July, October)

- American Gynecological Society. (1876) *President*, Emil Novak, Baltimore, Md. *Secretary*, Norman Miller, Ann Arbor, Mich. Annual meeting to be announced.
- American Association of Obstetricians, Gynecologists and Abdominal Surgeons. (1888) *President*, A. D. Campbell, Montréal, Quebec. *Secretary*, James R. Bloss, 418-11th Street, Huntington, W. Va. Annual meeting Hot Springs, Va., Sept. 4-6, 1947.
- Central Association of Obstetricians and Gynecologists. (1929) *President*, Earl C. Sage, Omaha, Neb. *Secretary-Treasurer*, John I. Brewer, 104 South Michigan Ave., Chicago, Ill. Annual meeting Louisville, Ky., Oct. 23, 24, and 25, 1947.
- South Atlantic Association of Obstetricians and Gynecologists. (1938) *President*, J. Randolph Perdue, Miami, Fla. *Secretary*, E. D. Colvin, 1259 Clifton Road, N.E., Atlanta, Ga. Annual meeting at Augusta, Ga., February 12 to 14, 1948.
- A. M. A. Section on Obstetrics and Gynecology. *Chairman*, William F. Mengert, Dallas, Texas. *Secretary*, A. B. Hunt, Mayo Clinic, Rochester, Minn. Annual meeting June, 1947.
- New York Obstetrical Society. (1863) *President*, Albert H. Aldridge. *Secretary*, R. G. Douglas, 530 East 70th St., New York City. Second Tuesday, from October to May, Yale Club.
- Obstetrical Society of Philadelphia. (1868) *President*, John B. Montgomery. *Secretary*, James P. Lewis, 1930 Chestnut St., Philadelphia, Pa. First Thursday, from October to May.
- Chicago Gynecological Society. (1878) *President*, Aaron E. Kanter. *Secretary*, Edward M. Dorr, 30 N. Michigan Ave., Chicago 2, Ill. Third Friday, from October to June, Hotel Knickerbocker.
- Brooklyn Gynecological Society. (1890) *President*, Alexander E. Dunbar. *Secretary*, William T. Daily, 142 Joralemon St., Brooklyn, N. Y. First Friday, from October to May, Kings County Medical Society, 1313 Bedford Ave., Brooklyn, N. Y.
- Baltimore Obstetrical and Gynecological Society. (1929) *President*, Lawrence Wharton. *Secretary-Treasurer*, John W. Haws, 9 E. Chase St., Baltimore, Md. Meets quarterly at Maryland Chirurgical Faculty Bldg.
- Cincinnati Obstetrical Society. (1876) *President*, Carroll J. Fairo. *Secretary*, Joseph G. Crotty, 136 West McMillan St., Cincinnati, Ohio. Third Thursday of each month.
- Louisville Obstetrical and Gynecological Society. *President*, Samuel S. Gordon. *Secretary*, J. B. Marshall, 605 Brown Bldg., Louisville, Ky. Meetings at the Brown Hotel every fourth Monday, from September to May, excluding December.
- Portland Society of Obstetrics and Gynecology. *President*, Ronald Frazier. *Secretary-Treasurer*, Gifford D. Seitz, 919 Taylor St. Bldg., Portland 5, Ore. Meetings last Wednesday of each month.
- Pittsburgh Obstetrical and Gynecological Society. (1934) *President*, Charles J. Barone. *Secretary*, Eugene A. Conti, 519 North Highland Ave., Pittsburgh 6, Pa. First Monday of October, December, February, April, and June.
- Obstetrical Society of Boston. (1861) *President*, Frederick J. Lynch. *Secretary*, Paul A. Younge, 1101 Beacon Street, Brookline, Mass. Third Tuesday, October to April, Harvard Club.
- New England Obstetrical and Gynecological Society. (1929) *President*, Arthur E. G. Edgelow, Springfield, Mass. *Recorder*, Carmi R. Alden, 270 Commonwealth Ave., Boston 16, Mass. Meetings held in May and December.
- Pacific Coast Obstetrical and Gynecological Society. (1931) *President*, Henry N. Shaw. *Secretary-Treasurer*, William Benbow Thompson, 6253 Hollywood Blvd., Los Angeles, Calif. Next meeting in Seattle, Wash., Oct. 1 to 4, 1947.
- Washington Gynecological Society. (1933) *President*, Lawrence Lee Cockerille. *Secretary*, Raymond T. Holden, 3111 16 Street, N.W., Washington 10, D. C. Fourth Saturday, October, November, January, March, May.
- New Orleans Obstetrical and Gynecological Society. (1924) *President*, Dr. Earl Conway Smith. *Secretary*, John S. Herring, Audubon Bldg., New Orleans 16, La. Meetings held October, November, January, March, and May.
- St. Louis Gynecological Society. (1924) *President*, Otto Krebs. *Secretary*, John E. Hobbs, 630 S. Kingshighway, St. Louis, Mo. Meetings second Thursday, October, December, February, and April.

*Changes, omissions, and corrections should be addressed to the Editor of the JOURNAL. The number after the Society's name is the year of founding.

The gradual progress and enlightenment must be viewed with mixed emotions until the process is complete. Already we know that criminal abortions and homosexuality are increasing in the Negro. The latter is a disturbing moral and mental factor in any group, and the former is bound to be an exacting factor in a people improperly nourished and already prone to infection. The stoicism, naturally happy and misunderstood disposition and zeal for life, give a false sense of well-being. Malnutrition, infection, anemia, tendency to cardiovascular disease, and environment are the more pertinent factors. The Negro and undernourished actually belie the generally accredited ability to "take it" obstetrically and surgically. We believe that once these women are admitted to a recognized hospital their treatment is comparable in competency to that of other localities. Certainly in our institution the house staff soon learns that the pathology and chance for learning are in this class patient, and the "private" patient is passed over in a zeal to stand by the patient with "real pathology." Bradford has insisted that the rural patient cannot be compared on a fair basis with her urban sister. The only consistent factors are poverty and sickness, and McCord has wisely said that uniformly good obstetrics cannot be given these women, when such care is measured in terms of professional service alone.

One has only to study the medical bibliography of this section to know that its obstetricians are cognizant of the problem of the late toxemia of pregnancy. It is unnecessary to mention the authors and their contributions.

The maternal mortality tables show that our section is usually in the higher third, and a review of the "cause of death" is indicative. The figures in North Carolina parallel those of the South Atlantic region. From tables published at about the time our studies begin we find:

| NEW YORK CITY COMMONWEALTH FUND | | NORTH CAROLINA BOARD OF HEALTH | |
|------------------------------------|------------|-----------------------------------|--|
| 17.5% | Abortion | 11% | |
| 25.0% | Sepsis | 15% | |
| 9.7% | Hemorrhage | 10% | |
| 12.0% | Toxemia | 41% | |

In 1933 Hamilton made a state survey, and his figures are given in comparison with Kosmak's.

| NEW YORK STATE—1,832 285 DEATHS | | NORTH CAROLINA—1,933 268 DEATHS | |
|------------------------------------|------------|------------------------------------|--|
| 30% | Sepsis | 19% | |
| 24% | Hemorrhage | 13% | |
| 23% | Toxemia | 43% | |

In a study of the years 1932 to 1936 the maternal mortality figure was 7.1 per 1,000 live births, with the toxemias accounting for approximately one-third of the deaths.

Deaths from toxemias of pregnancy (as recently reported by Lock and his Committee on Maternal Welfare):

| | |
|------------------------|-------|
| North Carolina | 32.5% |
| Buffalo (1935-40) | 10.0% |
| Philadelphia (1933-43) | 11.1% |
| Minnesota (1934-42) | 6.25% |

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South Atlantic Association of Obstetricians and Gynecologists

*Transactions of Annual Meeting
Savannah, Ga., Feb. 6 to 8, 1947*

PRESIDENTIAL ADDRESS*

Late Toxemias of Pregnancy; the Number One Obstetrical Problem of the South

ROBERT A. ROSS, M.D., F.A.C.S., DURHAM, N. C.

(From the Department of Obstetrics and Gynecology, Duke University Medical School)

THE problem of the "ill-fed," "ill-clothed," and "ill-housed" is not new in the South; nor is the menace of the toxemias of pregnancy. That these apparently diverse statements are related and pertinent is not too difficult to demonstrate.

Even though the mentally and financially able people of the South were motivated only by the most selfish instincts, they would realize the necessity of preserving the health and competency of this class. It is well recognized that these thirteen million persons are the greatest and probably the last source of man-power reserve. As a matter of fact, the thoroughly altruistic capable leaders have since Colonial days taken a genuine and helpful interest in these people. This has continued and progressed even through the devastation and misery of the Civil War. The enlightened class had not only to strive to survive themselves, but also to carry the less fortunate through all kinds of political, sociologic, and especially economic discrimination. The resulting rancor and bitterness are still manifest in the more stupid class of white people. To repeat the triad of "ills" is familiar.

McCord in scholarly fashion has called attention to the high maternal mortality and the social problems which confront the Negro and the large group of usually impoverished white population. In a recent study, Williams has shown that race per se should not be an altering factor.

*Presented at the annual meeting of the South Atlantic Association of Obstetricians and Gynecologists, Savannah, Ga., Feb. 6 to 8, 1947.

TABLE I. PRESENTATION OF DATA, DUKE HOSPITAL, 1931-1946

| | |
|---|-----------------------------------|
| Total deliveries | 11,000 |
| (Ratio white-Negro 8 to 5) | |
| Eclamptic state | 309 |
| (Convulsion = 203) | |
| (Nonconvulsion = 106) | |
| Deaths | 35 |
| (11.1% total) | |
| 15.2% = convulsion) | |
| Other toxemias | 1,493 |
| Deaths | 45 (or 3.7%) |
| Total toxemias | 1,802 or 16.3% of all deliveries. |
| Total deaths from toxemia | 80 (4.5%) |
| Percentage of total obstetric deaths = 38.2 | |

*Eclampsia Deaths**Age:*

16 patients = 15-20 years
 12 patients = 20-30 years
 7 patients = 30 plus

Parity:

18 patients = 0
 5 patients = 1-2
 5 patients = 3-5
 7 patients = 6 plus

Negro = 21
 White = 14

Prenatal Care:

19 patients = None
 5 patients = 1 visit
 9 patients = 3 visits
 1 patient = Fair
 1 patient = Good

(Only one regularly attended this Out Patient Clinic)

Convulsions Before Admission:

14 patients = 1-5
 10 patients = 5-10
 5 patients = 15 or more
 4 patients = None
 2 patients = Unconscious no information

Time From First Convulsion Until Admission:

4 patients = 1 to 3 hours
 8 patients = 3 to 4 hours
 13 patients = 5 to 10 hours
 7 patients = 10 plus hours

Distance travelled to hospital:

3 patients = Local (10-mile radius)
 5 patients = 15 miles
 6 patients = 25 miles
 9 patients = 35 miles
 5 patients = 50 miles
 7 patients = 60 plus miles

Delivered at home = 6

Undelivered = 8

Artificial rupture of membranes = 11

Low forceps = 2

Time from admission to delivery:

4 patients = 1 to 12 hours
 3 patients = 12 to 24 hours
 6 patients = 24 to 48 hours
 7 patients = 3 to 5 days
 1 patient = 5 to 7 days

Time in Hospital Before Death

1 patient = 15 minutes
 4 patients = 1 to 5 hours
 3 patients = 5 to 12 hours
 5 patients = 12 to 24 hours
 9 patients = 24 to 48 hours
 2 patients = 72 hours
 4 patients = 4 to 6 days
 7 patients = 7 to 20 days

Stillborn = 13

Viable Fetus = 14

Autopsies = 23, or 74.3 per cent

Hamilton studied 1,396 maternal deaths in North Carolina as related to the time of pregnancy that the pregnant woman first consulted a doctor, and found that 82.4 per cent of the total had some complication of pregnancy or concurrent disease when they first saw their physician, and that only 17.6 per cent reported for examination when they were presumably well. "If we assume that adequate prenatal care must begin before the end of the fourth month of pregnancy, 5.2 per cent gave their physician a fair chance to give them protection. In a second report, approximately 9 per cent of the small number included in that study reported to the physician before the end of the fourth month. It is evident that we have not yet made progress in our efforts to provide adequate prenatal care to those of our citizens who are creating new life."

Cooper, in his year's (1946) summary, states that in 1937 only 15.5 per cent of all births were in a hospital; in 1944, 51 per cent of the total births occurred in hospitals; and that 84.2 per cent of women who received E.M.I.C. care were delivered in hospitals (over 12,000). Lately, the picture has brightened. In North Carolina the total maternal mortality for 1941 to 1945 was 3.3 per cent, and for 1945 alone was 2.5 per cent. This, together with the low infant mortality of 43.4 per thousand live births, is most heartening.

That North Carolina is a rural state is readily shown when it is recorded that thirty-four counties have no hospital beds, and in fifty-five counties there is no bed for sick Negroes (there being a total of one hundred counties) and that in 1945 15,000 women were attended by midwives in a total of 85,000 live births. This is in the state where the first white "live birth" was recorded (also delivered by midwife according to Paul Green's book).

With no sharp demarcation there are three dietary groups of patients in North Carolina: (1) the intelligent economically capable, (2) the fairly co-operative adequately nourished, and (3) the uninformed improperly nourished medically inarticulate group. We have rarely found toxemia in the first two, but it is the prime factor in maternal mortality in the last.

We feel that the subsoil of toxemia of pregnancy is, paradoxically, prepared by improper dietary habits, usually lack of certain vitamins, minerals, and proteins, and by improper fluid intake and output. In our area such a patient would develop pellagra if exposed to the sun and, we feel, may develop symptoms of pregnancy toxemia if she becomes pregnant and does not present herself for treatment. Some of our findings are given support of this thesis. Whether simply parallel or actually causative is of little moment, when we realize that medical care will dispel the problem.

As soon as one sees a pregnant patient and starts any regulatory regime, that is prenatal care, and no one can stand by and allow a patient to develop toxemia symptoms.

The nearest approach to a control study is on the patient who is admitted with evidence of toxemia and who under diet, sedation and elimination is controlled but for some reason insists on leaving the hospital. The return to familiar domestic and dietary habits invariably leads to readmission, usually with more alarming symptoms.

Six of the patients had been delivered at home and eight died undelivered. Two patients were delivered by low forceps, these being the only operative deliveries.

Eleven patients had the membranes surgically ruptured. This procedure was done when the patient was in labor and delivery imminent, when the patient was thought to be stabilized and delivery thought to be desirable, or when the patient's condition progressively became worse and an effort was made to get the patient into labor. The incidence of infection in these patients was high (40 per cent), and two of them had gas bacillus infection post mortem. In the patients delivered there were nineteen viable infants and thirteen stillbirths.

The elapsed time from admission until delivery was one to twelve hours in four patients, twelve to twenty-four hours in three patients, twenty-four to forty-eight hours in six patients, three to five days in seven patients, and seven days in one patient. In the first and the last two categories we found most of the patients who had rupture of the membranes.

Similar information is obtained by listing the elapsed time from admission until death of the patient. One died within fifteen minutes, seven within twelve hours, five in twenty-four hours, nine in forty-eight hours, two in seventy-two hours, four within four to six days, and seven in a period of seven to twenty days. One patient was discharged and readmitted eighteen days post partum and died of urinary infection and empyema, but postmortem findings showed periportal degeneration of the liver. Another patient had a pulmonary embolus on the ninth postpartum day, but showed characteristic lesions of eclampsia.

Carter has reported the postmortem findings on these patients. It was only at this late investigation that we were able to classify accurately some of our toxemia patients. If the examination revealed the findings usually described in eclampsia, the patient was so classified. Certainly some of these fatalities are questionable. Because of the findings of the Smiths (increased gonadotropes with lowered estrogen assays) and the lesions usually described when the gonadotropes are increased (as chorionepithelioma), we were interested in the study of the ovaries and the pituitary for the possibility of increased luteinization of the ovary and anterior pituitary changes. Except for one patient who died without convulsing and in whom we found a basophilic adenoma of the pituitary and ovaries which were definitely hyperluteinized there were no other suggestive findings.

Discussion

On checking the localities from which our toxemia patients have been referred, and on reviewing the state morbidity and mortality statistics, we have found that in the same areas in which eclampsia occurred most often, we were likely to find a large percentage of pellagra and similar diseases. On close and repeated questioning and investigation we found that the patient that we see in eclamptic convulsions has come from the same group who subsisted on a diet similar to pellagrins. The diet is grossly deficient in all the vitamins, especially A, C, and D, as well as being inadequate in the minerals. The energy-producing

ANALYSIS

We have attempted to utilize the accepted classification for the late toxemias of pregnancy, but have found, as was anticipated, that often accurate classification is possible only on discharge of the patient. Our limited bed space prevents hospitalization of all but the severely toxic patients, and on discharge over eighteen hundred, or 16.3 per cent, of all patients delivered showed evidence of toxemia, as judged by a blood pressure of 140/90, albuminuria, and other findings. This figure at one time was over 30 per cent.

Our criteria for the eclamptic state are blood pressure 160/100, albuminuria, increased blood uric acid, and lowered CO₂ combining power associated with other usual findings. In this group we admitted two hundred and three patients with convulsions and 106 patients without convulsions. In the latter group four of the patients who later developed convulsions died. The death percentage in the eclamptic group was 11.1 per cent in the total and 15.2 per cent in those with convulsions. Nearly fifteen hundred patients had "other toxemia of pregnancy," the hypertensive and cardiovascular renal groups, the total mortality being forty-five, or 3.7 per cent. The total death from "late toxemia" being eighty or 4.5 per cent. These eighty deaths represent 38.2 per cent of all deaths in obstetric patients.

We have studied in detail the deaths of patients who had convulsions, knowing that there can be no doubt about the eclamptic state in such patients, and recording the death as a failure by someone somewhere in the course of the pregnancy. No effort nor desire is made to "correct" the mortality figure, however, a sincere effort is made to investigate it.

Seven of the thirty-five fatalities were in patients over 30 years of age, and twelve patients were para iii to para x, of whom two had previous eclamptic seizures, which indicates that the patient does not have to be a "young primipara." The inverse ratio of white and Negro patients is of interest. Our total deliveries have a ratio of eight white to five Negro, the deaths in this group is three Negro to two white.

The lack of prenatal care in this, as in other reports, stands out. Nineteen patients had not seen a doctor during the pregnancy until convulsions occurred. Five had made one visit to a doctor, nine had made three visits, one had "fair" prenatal care, and only one had care that was good. Only one patient had regularly attended our Out Patient Clinic.

Four patients admitted with the diagnosis of toxemia had not had convulsions, but three of them later convulsed. Two were unconscious and never regained consciousness; four had ten or more convulsions before admission (twenty-eight being the maximum), ten had five or more, and fourteen had one to five convulsions.

In seven of the patients ten or more hours had elapsed between the time of of convulsion and admission, thirteen had a lapse of five to fourteen hours, eight three to five hours, and four one to three hours.

To reach this hospital seven patients had to be transported over 60 miles (the longest distance being 150 miles), twenty over 25 miles, five, 15 miles, and only 3 had local residence.

the enlightened doctors and now have underway a program which should largely eliminate the menace of toxemia of pregnancy, the nutritional and other diseases which plague those who do not have recourse to medicinal care. Among the provisions are loans for medical students, utilization and coordination of all teaching facilities, utilization of all hospitals for interne and resident training, and rotation, peripheral postgraduate training, improvement of laboratory service, provision of consultation service, coordination of State wide medical care, integration of public health education and medical, expansion of the present two-year medical school at the State University, the building of hospitals where needed, and the alternate use of "Health Centers" where hospitals are not feasible. Such a program has particular appeal to the South and its traditional "States Rights" stand. It places squarely on the State its responsibility of aiding in the "ill" among its citizenry, a citizenry not recently favored by Federal grants and with notable exceptions, private philanthropy.

elements are adequate as a whole, but there is a protein deficiency. The animal protein consists chiefly of pork, which varies with the season. It is overabundant in the fall and winter, but inadequate in the summer. The largest proportion, estimated as 70 per cent, of the protein in the diet was furnished by the cereals and only approximately 30 per cent by meats, milk, and eggs. It is conceivable that, while the total amount of protein was adequate, the quality of the protein, or the quantity of the type of protein best suited for replacement of maternal tissue and blood proteins, was not entirely adequate. This possibility was borne out of the discovery of the relatively low plasma protein values. Also, on the basis of our knowledge of the group of the population from which most of the patients came, the dietary was very likely to have been deficient both in the quantitative and qualitative aspects.

In studying a group of such patients ante partum our figures for the plasma proteins in the fourteenth week ante partum agree fairly well with those found in the literature (ably reviewed by Dieckmann and Wagner) and show a general decrease as compared with values for normal nonpregnant women. This decrease is almost entirely at the expense of the osmotically more active albumin fraction, and is thus reflected in the figure for colloid osmotic pressure.

The lipin curves confirm in general the established tendency toward hyperlipemia in pregnancy. While, in common with other observers, large individual variations were found in our study of the total lipin, cholesterol, and phospholipid values, already considerably above normal levels at the beginning of our observations in the fourteenth week ante partum, tended to increase still further until parturition and fall to normal levels post partum. No striking differences were found which could be accounted for either on the basis of diet or of presence or absence of toxemic symptoms. The only general observation which can be made is that in pregnancy, as in other conditions involving hypoproteinemia, notably in nephrosis and in other forms of water retention, there appears to be a tendency toward a concomitant hyperlipemia. This may or may not be an expression of an attempt on the part of the organism to compensate for the fall in the colloid osmotic pressure due to the hypoproteinemia as suggested by Fishberg.

Aside from our own efforts in prevention and salvage of toxemia patients, it is gratifying to see the general purposeful efforts toward better prenatal care throughout this area. This state has for years sponsored lectures and refresher courses. Bradford, Hamilton, and the present Maternal Welfare Committee have reviewed the maternal deaths, a means that has been so brilliantly successful in New York, Philadelphia, Alabama, South Carolina, and other districts. The Board of Health has been especially helpful in checking birth certificates with female deaths and in having the County Nurse furnish additional information when the facts were vague or inconclusive. The State Medical Journal kindly allotted a page to the Committee, and each County Medical Society appointed a representative to confer with members of the Committee. In order to reach all citizens of the State, to inform them on health matters, and to provide facilities and personnel, a "Good Health" program has been instituted. Wise and humanitarian governors and legislators have listened to

of the composition and pharmacologic action of veratrum veride, that they do, indeed, know little about it. Bryant's original paper, reporting 121 cases, and describing his treatment of eclampsia by the use of veratrum veride and magnesium sulfate, recorded a maternal death rate of 9.9 per cent. Another report with Fleming³ as co-author appeared in 1940; this time there were 121 eclamptics treated by the same method with a maternal mortality of only 1.6 per cent. These results in two large series of cases were so much better than any published in America that the Boston Lying-in Hospital decided to adopt Bryant's program, and it is with the outcome of our small series of 32 cases that the present paper is concerned.

But, before we proceed further, let us gratify our curiosity about this "obsolete" and "useless" drug which is treated so cavalierly by Goodman and Gilman.

There are three plants belonging to the Lily family, which produce the so-called veratrum alkaloids. The first is *Veratrum album* Linnaeus, the white or European hellebore; the second is *Schoenocaulon officinalis* Gray, the sabadilla; and the third is *veratrum viridi* Aiton, the green or American hellebore. Each is interesting for a different reason. From the rhizomes or root-stocks of veratrum album seven alkaloids have been isolated; these are germerine and protoveratrine, which are known to be active; and jervine, rubijervine, pseudojervine, protoveratridine, and germine, which are believed to be inactive. Veratrum album is important because its active alkaloids have been employed in most foreign investigations. From the seeds of the sabadilla plant is obtained veratrine, an alcoholic extract, which contains two active alkaloids, cevidine and veratridine, and at least one inactive one, cevine. The sabadilla plant is noteworthy because cevidine and veratridine can be obtained in pure crystalline form; and veratridine is of special interest to us in Boston because with it Kraye of Harvard Medical School has conducted the only recent systematic study of the veratrum alkaloids. Veratrum veride is of outstanding importance because from its rhizomes is obtained veratrone, the only drug of the veratrum group now in clinical use in the United States. Although careful analyses of veratrum veride have not been made, it is supposed to contain essentially the same alkaloids as veratrum album, with the possible exception of protoveratrine. Veratrone has a stated composition of 0.25 per cent pure alkaloids. It is prepared by extracting the rhizomes with alcohol, and vacuum distilling this extract to obtain a solid mixture, which is assayed, probably by chemical and gravimetric methods. It is then made up to the stated weight per volume, and 0.5 per cent chlorbutanol is added as a preservative.

Out of the confusion created by a review of the pharmacologic literature these opinions emerge: Probably the fall in blood pressure and the slowing of the pulse which follow the introduction of veratrum into the circulation result from a reflex stimulation of the vagus arc (Cramer⁴). This stimulation begins in the chemosensitive afferent nerve endings in the auricles and passes to the medulla, where it acts upon the vasodilator center and the cardioinhibitory center. It then returns through the afferent fibers of the vagus, the vasodilator impulse passing to the peripheral arteries and arterioles, and the cardioinhibitory impulse to the heart again (Jarisch and Richter⁹). As long ago as 1867 von Bezold²² showed that cutting the vagus would prevent the effect of veratrum in lowering the blood pressure and slowing the heart rate. Recently Kraye and his co-workers^{10, 11} have devised an ingenious double dog experiment in which the heart of one animal is connected to its head only by its nerves.

THE TREATMENT OF ECLAMPSIA AND PRE-ECLAMPSIA WITH VERATRUM VERIDE AND MAGNESIUM SULFATE*

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THIRTY years ago the delivery of an eclamptic presented no problem to the obstetrician: according to his simple philosophy the woman was having fits because she was pregnant; if she ceased to be pregnant there would be no reason for her to have fits; therefore he emptied her uterus forthwith, usually by manual dilatation of the cervix followed by forceps, or by version and extraction. About 30 per cent died, usually from shock and hemorrhage. As cesarean sections became more common they were performed on eclamptics, but with even worse results, for the death rate then rose to 40 per cent. In the middle 1920's, however, two articles appeared which changed the attitude of thoughtful obstetricians from radicalism to conservatism and have been the indirect means of saving many lives.

Strogonoff¹⁰ reported in 1926 a series of 300 personal cases, treated with morphine, chloral, and chloroform, and without active immediate interference, with a mortality of 2.6 per cent. Investigation, however, showed his Russian cases to be far milder than American eclamptics; in fact, many of his patients appeared to be merely advanced pre-eclamptics. The year before Lazard¹² had published a paper, also on the conservative treatment of eclampsia, in which he described the control of convulsions with the intravenous use of magnesium sulfate. He reported 20 cases with a mortality of 10 per cent. No American clinic which copied Strogonoff's regime was able to obtain results comparable with his as he had reported them. On the other hand, the use of magnesium sulfate, either intravenously or intramuscularly with or without sedatives, has become almost standard practice in large American clinics, although the results are not always all that might be desired. But, at any rate, we have learned that active interference with an antepartum eclamptic during her crisis of convulsions and coma is apt to end in disaster. If, on the other hand, we wait until the convulsions have ceased, the coma has passed off, and there is an adequate output of urine, we can induce labor by some simple means with much greater safety.

In 1935 Bryant² exposed to public view an old drug which in most drug-stores except those of Cincinnati had been accumulating dust on the back shelves. This drug is veratrum veride, described by the authors of a popular work on pharmacology as "practically obsolete today and enjoying a well-deserved oblivion."

Pharmacologists, like other people, are apt to say that a thing is no good if they know little about it, and it will be evident when we consider their accounts

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puted means, "a remover of obstructions, and a medicine to cause blisters and to be snuffed into the nose." He also described it as an acrid narcotic and emetic—which is plain enough—but he also made the fundamental and original observation that when it was taken internally it caused the pulse to be "small, compressible, and infrequent."

The next important figure in the history of veratrum veride was Norwood of Cokesbury, South Carolina, who devised the famous Norwood's tincture, which he first described in 1852. He manufactured it on a commercial scale and issued a prospectus which gave instructions for its use, quoted case histories, and ended with testimonials. That Norwood held a favorable opinion of his product is evident by this quotation from his prospectus of 1856.

"But when the unsurpassed value of the remedy is brought into account; when it is known that it possesses powers that cannot be supplied by any and every agent of the *Materia Medica*, singly or combined; when it is known that it is the only agent by which we can say to the tumultuous and tempest tossed heart in febrile and inflammatory diseases, be still, and lo all is quiet, and this wayward organ grows calm in all its actions, and the vital fluid flows smoothly and gently through all its channels, the price sinks into insignificance."

Aside from its use as a cardiac tonic it was also employed, and still is in some parts of the United States, in pneumonia and other febrile diseases.

Credit for the first use of veratrum veride to control the convulsions of eclampsia belongs to Baker¹ of Eufala, Alabama, who, in 1860, gave it to one patient with a successful result.

From then on veratrum veride was used sporadically in eclampsia and scattered reports appeared in the literature. It was not until 1895, however, that Reamy¹⁷ founded the veratrum school of Cincinnati of which the work of Bryant is the lineal descendant. Worthy of mention, however, is the paper of Mangiagalli¹⁴ of Milan, whose report appeared in England in 1908. He recorded 100 cases with a mortality of 12 per cent, whereas his death rate for the previous ten years had been 24 per cent.

Procedure

The general routine treatment for eclampsies at the Boston Lying-in Hospital follows in the main that of Bryant and Fleming. The patient is placed in a quiet, darkened room with a nurse in constant attendance. Morphine, one-fourth grain, demerol 100 mg. subcutaneously, or 3 drams of paraldehyde in 2 ounces of mineral oil are used to control restlessness, but are not given routinely. Five minims of veratrone are given hypodermically on admission. Veratrone is repeated as is necessary in 5 to 10 minim doses at twenty-minute intervals to keep the blood pressure below 150 systolic and the pulse below 80, or if there is a convulsion.

Magnesium sulfate in 50 per cent solution is given intramuscularly into the buttocks in 10 to 20 c.c. amounts every four to six hours. Magnesium depresses the central nervous system and the peripheral neuromuscular apparatus so that the excitation of voluntary muscle by nerve impulses is prevented. Magnesium depresses all portions of the central nervous system which leads to the loss of reflexes and a continuous fall in blood pressure. It also affects the heart muscle and produces bradycardia.

Two-hundred fifty cubic centimeters of 25 per cent glucose in buffered sterile water are given slowly every four hours if the patient is unconscious. If she is conscious it is given every six hours. The purpose of this is to encourage urinary secretion. In a few instances we have found the use of salt-poor albumin in 50-gram doses to be followed by a marked increase in urinary output and the disappearance of edema. Our results with plasma have not been so

Its heart receives blood from another dog through a constant perfusion pump. When veratridine is injected into this heart—isolated in a vascular sense but still in nervous communication with the head—the blood pressure in the head falls, thus demonstrating that reflex vasodilatation originates in the heart. In the opinion of most pharmacologists, this explanation of the action of veratrum is the correct one. Recently however, Willson and Smith,²¹ using veratrone, reported that they had produced vasodilatation by perfusion experiments in the isolated ear, kidney, and leg of rabbits, thus suggesting a local effect on the blood vessels. Moreover, they administered veratrone to vagotomized dogs and produced a distinct hypotension without a drop in pulse rate, although the fall in blood pressure was much less than when the vagi were left intact. This, they reasoned, indicated that afferent vagal reflexes are unnecessary for peripheral dilatation.

Although these results appear conflicting, it must be remembered that Krayner used veratridine, an alkaloid obtained from *sapadilla* for experimental purposes and never employed in clinical medicine, while Willson and Smith conducted their experiments with veratrone, the only preparation of veratrum readily available at present in the United States for therapeutic use. It should also be recalled that the alkaloids of veratrum veride, of which veratrone is a preparation, have never been completely isolated. They are assumed to be about the same as those in veratrum album, although there is no proof that they are. If the investigators working on this problem would employ the same substance for their experiments, it is likely that these results would be less at variance, and of more practical value to obstetricians.

So far no pharmacologist seems to have evinced the slightest curiosity about the anticonvulsant action of veratrum, although it is this effect which interests the practitioner most and it is the only one of any lasting benefit to the patient. Lacking scientific proof, however, we as clinicians may assume that the vasodilatation caused by veratrum relieves the cerebral anemia and edema which are supposed to cause the convulsions and coma of eclampsia.

Before leaving the pharmacology of eclampsia one should mention the toxic effects of overdosage. These are: vomiting; burning sensations in the mouth, throat, and stomach; profuse sweating; giddiness; headache; and in some cases relaxation of the vesical and anal sphincters. Therefore the initial intramuscular dose of veratrone in our clinic is restricted to 5 minims and is increased as conditions warrant.

Hellebore, from which veratrum is derived, has been known since the Middle Ages. In medieval times it was used to protect cattle from evil spirits, and the rootstalks employed for this purpose were dug up to the accompaniment of mystic rites. Sorcerers, when they wished to make themselves invisible, sprinkled themselves with the powdered substance. The American Indians, on the occasion of selecting a new chief, made an extract of hellebore and gave it to the young braves; and the one who vomited the least was made head of the tribe. Apparently he who had the strongest stomach was judged to have the stoutest heart. The early New England settlers used it as a crow poison, and horticulturists have long employed it as an insecticide.

Probably the first physician in America to use veratrum veride as a medicine was Osgood¹⁶ of Providence, Rhode Island. He described it somewhat obscurely as a "deobstruent, epispastic, and errhine," which being inter-

magnesium sulfate by mouth to free watery catharsis, and are given a diet of 145 Gm. protein, 220 grains carbohydrate, 100 grains fat, and salt is restricted to 1.6 grains. This total is 2,200 calories. If there is a sudden hypertension, if the albumin increases notably, or if the patient develops symptoms of toxemia she is given 50 per cent magnesium sulfate intramuscularly in 10 c.c. doses every six hours for four doses, then every twelve hours for four doses, accompanied by veratrone in 5 minim doses sufficiently often to produce a fall in blood pressure.

Fig. 1 shows the maternal death rate by five-year periods from 1873 to the present day. The double vertical line marks the beginning of the veratrone-magnesium sulfate regime.

'73-'77-'82-'87-'92-'97-'02-'07-'12-'17-'22-'27-'32-'37-'42-'46

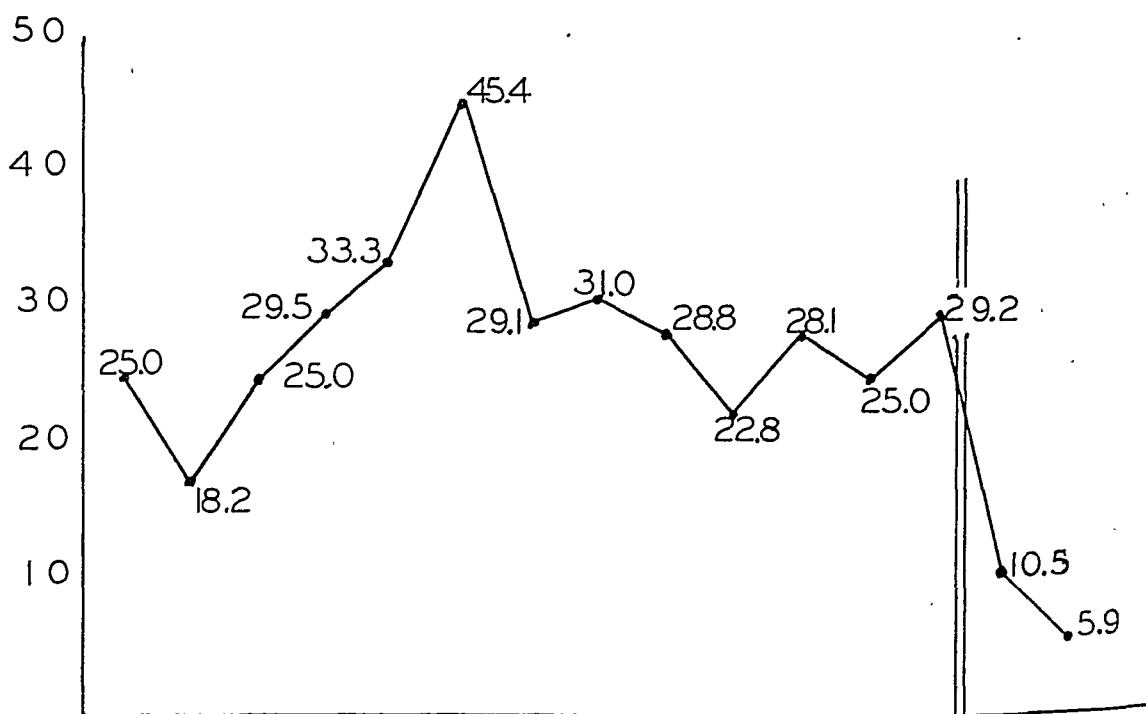


Fig. 1.

TABLE I.

| | CASES | DEATHS | PER CENT |
|--|-------|--------|----------|
| <i>Magnesium sulfate</i> | | | |
| Lazard | 103 | 14 | 13.6 |
| Dorsett | 190 | 13 | 6.8 |
| Rucker | 129 | 6 | 4.6 |
| | 422 | 33 | 7.8 |
| <i>Veratrone with or without Magnesium sulfate</i> | | | |
| Houltaim | 14 | 2 | 14.3 |
| Greene | 14 | 0 | 0.0 |
| Harkins | 14 | 0 | 0.0 |
| Bryant | 121 | 12 | 9.9 |
| Bryant and Fleming | 120 | 2 | 1.6 |
| Boston Lying-in Hospital | 32 | 2 | 6.2 |
| | 315 | 18 | 5.7 |

satisfactory. Enough parenteral fluid is given to prevent dehydration and not enough to cause edema. If the patient is conscious she is given 2,000 to 2,500 c.c. of water every twenty-four hours.

Pregnancy is terminated only after the convulsions have ceased and an interval of twenty-four to seventy-two hours has elapsed. If the cervix is partially effaced and dilated enough to admit one or more fingers, the membranes are artificially ruptured; if not, a Voorhees bag is introduced. Cesarean sections are performed only on strictly obstetric indications, such as cephalopelvic disproportion or placenta previa. No cesarean sections were performed in our series upon antepartum or intrapartum eclamptics. Once induced, labor is allowed to proceed normally and to terminate, if the presentation be a vertex either by normal delivery or low forceps. Ether with oxygen is usually employed in normal deliveries; low spinal anesthesia for operative deliveries.

Results

Using this method, we have treated 32 eclamptics from 1940 to 1946, inclusive. Eighty-one and two-tenths per cent were primiparas. Convulsions occurred antepartum in 20 cases, or 62.5 per cent; intra partum in 5, or 15.6 per cent, and post partum in 7, or 21.9 per cent. Eleven patients had 1 fit, twelve patients had 2, one had 3, one had 4, one had 5, two had 6, one had 8 fits, one had 9, one had 13, and one had 14 fits. Six were comatose. In a detailed study of 18 of these cases Tower found the average normal blood pressure in those instances where it could be obtained to be 117/74 with a maximum rise to an average of 185/113. The average fall in blood pressure was 86/52, with an average dose of 10 minims of veratrone in an average time of forty-two minutes. The average maximum slowing of the pulse rate was 48 beats per minute. These 18 patients received an average of 11 to 12 doses, with an average total of 62 minims (about 4 c.c.). The greatest degree of albuminuria in the 32 patients was as follows: grade 4, 52.1 per cent; grade 3, 31.1 per cent; grade 2, 16.8 per cent.

Labor was induced in 18, or 55.6 per cent, of the cases; nine times by artificial rupture of the membranes, and in the remaining nine by the dilating bag.

There were 33 infants, including one pair of twins. Twelve infants were delivered normally and eleven by low forceps, these two methods making 71.7 per cent of the total. The remainder were delivered as follows: Braxton Hicks version (on nonviable infants) 5, breech extraction 3, Willett's forceps after Dührssen's incisions, one. One pre-eclamptic developed a convulsion after a cesarean section.

There were two maternal deaths, giving a mortality rate of 6.3 per cent. Both were neglected emergency cases admitted from small outside hospitals; both were moribund on entrance and died soon afterwards. Sixteen, or exactly 50 per cent, of the eclamptics were emergency cases. During the years 1940 to 1946 under study there were 18,686 deliveries in the public wards of the Boston Lying-in Hospital. The frequency of eclampsia in the registered clinic cases was once in 1,161 deliveries, and none of these eclamptics died. This speaks well for the value of prenatal care, and again emphasizes the truism that there can be no comparison between prevention and cure.

Eighteen, or 54.5 per cent, of the 33 infants were discharged alive; 13, or 39.2 per cent were stillborn; and 2, or 6.3 per cent, died. Nine of the thirteen stillborn infants weighed under 4 pounds. The total fetal mortality was 45.5 per cent.

The treatment of severe pre-eclamptics follows the same principles in a modified form. All pre-eclamptics of any degree are kept in bed, are given

MYCOTIC VULVOVAGINITIS AND THE VAGINAL FUNGI*†

A Report of 280 Patients

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INFECTION of the vulva and vagina, with certain of the nonascosporogenous, mycelial producing, yeastlike fungi, is a common cause of pruritus vulvae, vulvovaginitis, dysuria, and increased vaginal discharge. Infection is most common during the childbearing age. Pregnancy and diabetes are said to be predisposing factors to infection.

Prior to 1931, mycotic vulvovaginitis was not regarded as common, and only isolated reports appeared in the literature. At that time, Plass, Hessel-tine, and Borts¹ reported a large series of patients and directed attention to the frequency of the infection. They also gave accurate descriptions of the symptoms and clinical findings.

In recent years mycotic vulvovaginitis is more frequently recognized, and the belief is now firmly established that these infections rank with the trichomonad syndrome as a common cause of vulvovaginitis.

The incidence of mycotic disease of the vulva and vagina varies in proportion to the recognition of symptoms and to the facilities used for diagnosis. The failure to utilize simple methods of culture, in conjunction with intelligent interpretation of the mycologic findings, often leads to improper diagnoses and subsequent improper treatment.

Unlike trichomoniasis, the diagnosis of mycotic vulvovaginitis is occasionally made difficult by the presence in certain vaginas of saprophytic fungi which closely simulate pathogens, but are incapable of initiating symptoms. These fungi cannot be differentiated from vaginal pathogens without the use of cultural methods. Furthermore, it is well recognized that patients may carry potentially pathogenic fungi in the vagina for long periods without evidence of symptoms. A clearer understanding of the symptoms, clinical findings, as well as of the mycologic flora of the normal vagina, makes this problem less confusing.

The Vaginal Fungi

Almost without exception, fungi isolated from the vaginas or vulvas of the symptomatic, as well as asymptomatic, patients fall into a large group which is referred to as yeasts or yeastlike. The yeasts or yeastlike fungi reproduce by budding, by the formation of a septate mycelium, and in the true yeasts the formation of a sexual phase called asci.

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Table I shows some collected statistics comparing the results obtained with magnesium sulfate alone with those attending the use of veratrone with or without magnesium sulfate. Although the results in both collections of cases are good, the advantage appears to be with the veratrone group. For a number of years at the Boston Lying-in Hospital our main reliance was on magnesium sulfate alone given intravenously after the technique of Lazard.¹³ Our results have been so much more satisfactory since we instituted Bryant's method that we shall probably continue to use it until something better appears.

Conclusions

In conclusion, it should be emphasized that no treatment will cure the grossly neglected eclamptic who arrives at the hospital breathing her last. The damage has already been done; nothing will save her life.

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The *Cryptococci*, or simple yeastlike fungi, occur in the vagina as yeast cells. Reproduction on corn meal agar, carrot plugs, and on Sabouraud's agar, is by budding or the formation of more yeast cells. Mycelia or ascospores are not produced under any conditions of growth.

At the present time there is no conclusive evidence of the pathogenicity of *Cryptococci* isolated from the vaginas or vulvas.

True cryptococcosis is a subacute or chronic infection of the lungs, skin, brain, or meninges and is due to an encapsulated species of *Cryptococcus* known as *Cryptococcus neoformans*. Benham and Hopkins⁶ have shown that non-pathogenic *Cryptococci* can be isolated from normal skin, mucous membranes, etc. Specific identification of *Cryptococcus neoformans* can be made by capsule identification and animal pathogenicity studies. The common vaginal *Cryptococci* do not form demonstrable capsules.

The true yeasts, or *Saccharomyces*, occur in vaginas as yeast cells. Cultivation on Sabouraud's agar usually produces only budding forms. Cultivation on carrot plugs or other suitable media results in the formation of the sexual phase or ascospores.

In our opinion both the vaginal *Cryptococci* and *Saccharomyces* assume importance only because they can so closely simulate and must be differentiated from species of *Candida*.

The genus *Candida* reproduces by the formation of yeast cells and the production of a vegetative mycelium. Both forms are frequently seen in the direct examination of vaginal discharge. If the material is from the vagina, the presence of mycelia by direct examination is presumptive evidence that the fungus belongs to the genus *Candida*. However, the finding of only yeast cells does not rule out the genus *Candida* or suggest either *Saccharomyces* or *Cryptococci*.

Cultivation on Sabouraud's agar produces yeast cells and a stage not easily differentiated from other yeasts or yeastlike fungi. Mycelium production on this medium is not consistent, and when it occurs on slants of Sabouraud's agar it does so only in the upper dried portion of the medium. In poured plates of corn meal agar, or on plates which after inoculation are overlaid with molten agar, mycelial production, at room temperature, occurs in from twenty-four to forty-eight hours.

Identification of Species Within the Genus *Candida*

The identification of species within this genus is based on biologic tests in combination with microscopic morphology and macroscopic colony formation. In 1938, Jones and Martin⁷ described methods of classification which were primarily bacteriologic and were based upon the study of fifty-nine strains of *Candida* isolated from the vaginas of patients in our clinic.

In Table I are shown the species of *Candida* commonly isolated from the vagina or vulva and the necessary criteria for identification. For a more detailed description of these methods reference should be made to previous reports.⁷⁻⁹

There have been few studies made on the classification of the genus *Candida*, in which fungi isolated from vulvas and vaginas were used to the exclusion of fungi from other sources. Plass, Hesseltine, and Borts,¹ in their original paper on mycotic vulvovaginitis used Castellani's¹⁰ classification. In later studies Hopkins and Hesseltine¹¹ expressed doubt concerning the accuracy of Castellani's methods and studied seventy-three additional strains of *Candida* by comparison with types 1, 2, and 3 of Stovall and Bubolz.¹² Only sixty-nine of these strains were regarded as classifiable, and sixty-seven were said to be type 2 of Stovall and Bubolz which is synonymous with *Candida albicans*.

When grown on Sabouraud's agar, at room temperature, most of the yeasts or yeastlike fungi show similar colony formations and types of growth. Separation of the different genera, three of which commonly occur in the vagina, is based on morphology when the fungi are grown on special types of media, as corn meal agar for mycelial production, and carrot plugs for the production of asci. This method first proposed by Ota² in 1924 separates the vaginal group into *Saccharomyces*, *Cryptococcus*, and *Monilia*.

Since the generic terminology is determined by priority of usage, the name *Monilia* as applied to the anascosporogenous, mycelial producing, yeastlike fungi is known to be incorrect. According to Conant³ and others who have reviewed the taxonomy, "The first mention of *Monilia* was that of Hill,⁴ 1751, for the forms described by Michelli,⁵ 1729, under *Botrytis* and *Aspergillus*."

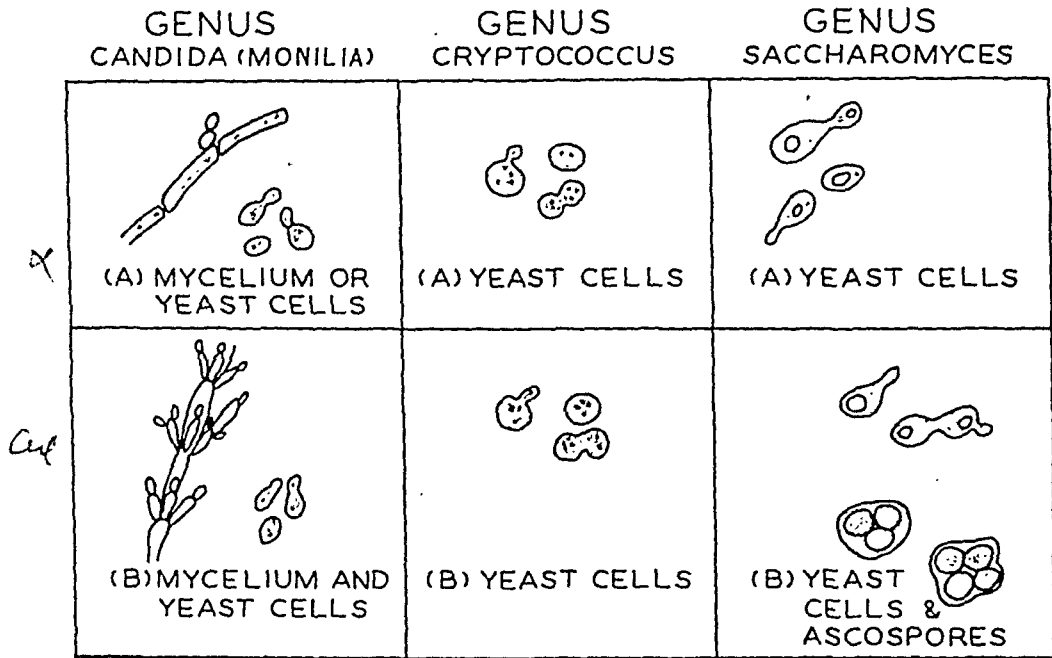


Fig. 1.—Generic Classification of the yeasts and yeastlike fungi from the vulva and vagina. The generic classification is based on morphology under special conditions of cultivation, i. e., corn meal agar for the formation of filamentous mycelium, carrot plugs for the formation of ascospores.

(A) Direct preparation from patient.

(B) In culture from corn meal agar and carrots.

In addition to *Monilia* a number of incorrect generic terms has been applied by different workers to this group of fungi. The confusion has been so great, that in 1939, at an informal meeting of Medical Mycologists at the Third International Congress for Microbiology, it was voted to substitute the name *Candida* for *Monilia*. It was the opinion of this group, that the existing confusion would be clarified if workers in this field would use only one generic term while awaiting official action of the International Botanical Congress. Consequently, the generic term *Candida* is now preferable and we prefer this term in our teaching and it is used in this paper.

This ruling rendered obsolete terms as monilia vaginitis and moniliasis of the vagina and vulva. However, since fungi belonging to the genus *Candida* seem to be the only fungi commonly involved in the production of vulvovaginitis, we prefer the term mycotic vulvovaginitis.

Differentiation of Genera

In Fig. 1 is shown the morphology of the three genera of common vaginal and vulvar fungi as they occur in the vagina and on special culture media.

renal glycosuria of pregnancy, and low pH of the vaginal secretions has been stressed by different observers. It has been shown also that dissociation may occur in strains of *Candida albicans* which have been maintained for long periods on artificial media, and that this dissociation, with the resultant loss of animal pathogenicity, can be produced at will by the use of certain chemicals.^{9, 15} Liston and Chisholm¹⁶ believe that in the pregnant female glycosuria plays an important part, and that this should be considered when treating this type of patient. This is in agreement with Hesseltine's and Campbell's¹⁷ belief that the yeastlike fungi are the etiologic agents in the vulvovaginitis so frequently seen in patients with diabetes mellitus. It is our experience that in patients with diabetes and vulvovaginitis the incidence of yeasts and yeastlike fungi is extremely high. On the contrary, there are some patients in whom the vulvovaginitis cannot be explained on the presence of fungi.

As previously stated, freshly isolated strains of *Candida albicans* are pathogenic when inoculated intravenously in rabbits. This has been shown by Benham,¹⁸ Stovall and Pessin,¹⁰ and many others. Stovall and Pessin also found that *Candida tropicalis* would kill rabbits if enormous doses were used. Other vaginal fungi are nonpathogenic for rabbits. Rabbit pathogenicity is perhaps the most important differential point between *Candida albicans* and *Candida stellatoidea*.

The first successful human vaginal inoculation reported was that of Haussman,²⁰ who used the vaginal discharge from an infected patient to inoculate a pregnant female. Hesseltine, Borts, and Plass,¹³ in 1934, inoculated eighteen patients with pure cultures of two species of *Candida*. They were successful in establishing infection in twelve. The two species were classified according to Castellani's¹⁰ classification as *Monilia pinoyi* and *Monilia metalondinensis*. They were successful also in producing oral thrush in newborn infants with *Monilia pinoyi*, but were not successful with *Monilia Krusei* or *Saccharomyces cervisiae*. *Monilia pinoyi*, *Monilia metalondinensis* and *Monilia Krusei* have been studied by Martin and Jones.⁹ The first two are synonymous with *Candida albicans* and the third with *Candida Krusei*. Bland, Rakoff, and Pincus,¹⁴ in confirming the results of Hesseltine and his co-workers, used strains isolated from patients with mild, moderate, and severe vulvovaginitis. The opinion expressed by these authors was that methods of classification answered no useful purpose. We therefore have no data on their strains other than the source of isolation.

Differential Diagnosis

Mycotic vulvovaginitis must be differentiated from trichomoniasis, non-specific bacterial vulvovaginitis, cervicitis, specific bacterial infections, chemical vulvovaginitis, atrophic vulvitis and vaginitis, leucoplakia, neurodermatitis, enterobiasis, pediculosis, or any disease or condition which produces pruritus vulvae or ani.

Differentiation should be made between, (1) those patients who harbor harmless saprophytic fungi in the vaginas or on the vulvas; (2) those patients who have positive cultures for potentially pathogenic species, but are asymptomatic at the time of culture; and (3) the symptomatic patients with a positive culture for species known to produce symptoms.

The physician who treats only the patients with obvious signs and symptoms misses many diagnoses of mycotic vulvovaginitis. Many patients are seen on whom the diagnosis is not obvious and can be made only by culture and by study of the fungus present. Pruritus is a frequent complaint in many varieties of vaginal and vulvar disease.

TABLE I. SPECIES CLASSIFICATION OF THE GENUS *CANDIDA* (MONILIA) CONTAINING VAGINAL PATHOGENS

| | SURFACE GROWTH SABOURAUD'S BROTH* | COLONY TYPE BLOOD AGAR† | CARBOHYDRATE FER- MENTATIONS‡ | MORPHOLOGY CORN MEAL AGAR | RABBIT PATHOGEN- ICITY |
|-----------------------------------|--|--|---|---|------------------------------|
| <i>Candida albicans</i> | Negative | Grayish Large Round Smooth border | Dex AG Sacch A Lact - Malt AG | Numerous Chlamydo- spores | Positive |
| <i>Candida stella- toidea</i> | Negative | Stellate | Dex AG Sacch - Lact - Malt AG | Chlamydospores | Negative |
| <i>Candida tropicalis</i> | Bubbly | Grayish Large Round Mycelial fringe | Dex AG Sacch AG Lact - Malt AG | Abundant my- celium | Slight (Stovall) |
| <i>Candida Krusei</i> | Heavy film | Small Irregular in size | Dex AG Sacch - Lact - Malt - | Spores ar- ranged like crossed sticks | Negative |
| <i>Candida para- krusei</i> | Negative | Small Round White | Dex AG Sacch - Lact - Malt - | Not distinctive | Negative |

*Incubated 48 hours at 37°C.

†Incubated 10 days at 37°C.

‡AG = Acid and Gas; A = Acid; - = Negative.

As stated in the table given by the authors, the sixty-seven strains listed as type 2 rarely formed acid in saccharose. Since one of the differential points between *Candida albicans* and *Candida stellatoidea* is the ability of the former to form acid in saccharose, it is possible that the sixty-seven strains were in reality both *Candida albicans* and *Candida stellatoidea*.

In the original paper of Jones and Martin⁷ a new species of *Candida* isolated from vaginas was described. Since this fungus seems to be common only in vaginas and has undoubtedly been previously identified with *Candida albicans* the reasons for separating these two species are repeated here: (1) When grown on pH 7.4 beef extract sheep's blood agar plates at 37° C., for twenty-four hours the inoculum taken from a forty-eight hour culture in Sabouraud's broth, the rate of growth is different. Fairly luxuriant growth of *Candida albicans* occurs; the growth of *Candida stellatoidea* is much less luxuriant. (2) When freshly isolated strains of *Candida albicans* were injected intravenously into rabbits, death of the rabbits occurred in four to five days. Freshly isolated strains of *Candida stellatoidea* failed to kill rabbits when twice the lethal dose for *Candida albicans* was injected. (3) Slight differences in carbohydrate fermentations occur. (4) Slight differences in colony type are found when the fungi are grown on pH 7.4, beef extract, sheep's blood agar plates at 37° C.

Pathogenicity of Genus *Candida*

The pathogenicity of certain of the vaginal fungi belonging to the genus *Candida* has been proved. Reports on the production of symptoms by the experimental inoculation of the vagina with pure cultures has been uniformly successful.^{13, 14} On the other hand, the mechanism whereby symptoms are produced in some patients while symptoms are absent in other patients who carry in the vagina the same species of *Candida* is still not understood. The role played by individual sensitivity, variations in pathogenicity of fungi of the same species, high glycogen content of the vaginal mucosa, diabetes mellitus,

The Fresh Preparation.—We have found that the direct microscopic examination of a saline suspension of the collected material is far superior to either a stained smear or the use of KOH or NaOH solutions as used in the demonstration of the skin fungi. For the direct examination, the discharge is collected on sterile swabs. Approximately 1 c.c. of physiologic saline is added, the swabs are twirled in the saline, the suspension poured on a glass slide, covered with a cover glass, and examined microscopically with the low power objective. With experience the mycelial forms of the genus *Candida* are easily seen with the low power objective, and can be recognized with certainty with the higher power. The yeast cell or budding stage is not easy to recognize with the low power. The saline suspension also has the added advantage that trichomonads can be searched for in the same specimen.

Culture.—In a large number of patients fungi are not demonstrable by direct examination. This is particularly true in patients with a mild infection or the typical patient who takes a douche before visiting the doctor. In these patients cultures offer the only reliable method of diagnosis. All of the yeasts or yeastlike fungi which might be present grow readily on Sabouraud's agar slants at room temperature in from forty-eight to seventy-two hours. This makes culture so simple that it can be routinely employed, even in office practice, without a great deal of effort. The increase in the number of positive diagnoses in patients with obscure pruritus would certainly seem to justify this procedure.

The Intradermal Skin Test.—The use of a vaccine as a diagnostic procedure in skin testing patients suspected of mycotic vulvovaginitis is of little or no value. Carter, Jones, Thomas, and Ross,²¹ in 1940, showed that the incidence of fungi in the vaginas of the patients with negative skin tests was as high as in the patients with positive tests. Vaccines, however, are occasionally of some benefit in treating patients with marked sensitivity or who fail to respond to other types of therapy. In these patients skin testing prior to the administration of vaccine, as an indication of the correct dosage, is a justifiable procedure.

Agglutination.—The presence or absence of low titered agglutinins bears little, if any, relationship to the presence of fungi in the vagina.²¹ This fact would be expected because of the high incidence of yeastlike fungi in normal stools, in the mouths of normal individuals, and the number of "carriers" of these fungi in the vagina.

Treatment

Treatments of these infections have included x-ray and ultraviolet light, various types of therapy in the form of douches, powders, and salves. One of the greatest problems in the treatment of vulvovaginal mycotic infection is the avoidance of overtreatment, and the ability to determine where the fungus infection ends and the x-ray or chemical vulvovaginitis begins. The sensitivity of vulvar tissue and vaginal mucosa to strong chemicals is well known, and must always be kept in mind regardless of the treatment used. The dread of the gynecologist is the referred patient with vulvovaginitis which has been overtreated.

Most of the treatments in use require daily or bidaily office visits, are time consuming for the physician, and end too often with an unsatisfied patient. In our opinion x-ray is contraindicated in all types of vulvar disease. Furthermore, the treatment of the vulva fails to take into account the source of the infection, the vagina.

Symptoms

The symptomatology is fairly clearcut and much may be learned by proper and detailed questioning of the patient. The primary, the most common and the essential complaint is *pruritus vulvae*. A fungus etiology should be considered in all patients in the menstruating age with this complaint. The degree of pruritus varies considerably in intensity and many patients report periods of relief followed by exacerbations. In severe infection the itching may be more intense than that experienced in any other type of vulvovaginal disease. The high incidence of yeasts and yeastlike fungi in the vaginas of asymptomatic patients makes the treatment of patients who do not have pruritus an unwise procedure. In contrast to the patients with the trichomonad syndrome and nonspecific bacterial vulvovaginitis, many patients with mycotic vulvovaginitis state that they have some relief from the pruritus during their menstrual periods. This is probably due to the alkalinity of the menstrual blood. Other common complaints which are secondary to pruritus are irritation and soreness of the vulva and introitus with associated dyspareunia. Dysuria is another common complaint and occurs in the form of external burning due to the urine passing over the irritated vulvar areas. Increased discharge, although a common complaint, when due to the actual fungus infection is practically always preceded by pruritus. The complaint of discharge without associated pruritus should lead one to suspect some other cause. Patients also frequently complain of swelling and breaking out around the vulva or of a feeling of heat.

Clinical Findings

By far the most helpful physical finding is the presence of a white, flaky, or cheesy vaginal discharge. This discharge can occur around the labia minora, clitoris, in the vagina or on the cervix. When this discharge is detected it should be collected carefully for direct microscopic examination and culture. Vaginal and vulvar findings vary from apparently normal to a diffuse hyperemia of the vagina, cervix, and vulvar areas. In severe infections a granular type of vaginitis may be present. The vagina may bleed easily on touch. Slight edema of the vulva is seen frequently and acute edema is not uncommon. The edema subsides rapidly after therapy is started. Cutaneous lesions as an extension from the vagina are not common, but are occasionally seen.

Diagnosis

Since the yeasts or yeastlike fungi are the only group of fungi which commonly occur in the vagina, much valuable information can be obtained from the careful microscopic examination of a fresh saline suspension of vaginal discharge. In obtaining material for examination, great care should be taken to collect the cheesy or flaky discharge when present. We have found it a good practice to start at the introitus and collect any suspicious discharge as the speculum is inserted. Once the speculum has been inserted the posterior, anterior and lateral walls of the vagina should be carefully inspected. Careful inspection and collection greatly increase the chances of diagnosis both in the direct microscopic examination and in culture.

TABLE II. YEASTS OR YEASTLIKE FUNGI ISOLATED FROM THE VAGINA AND VULVA OF 200 OBSTETRIC PATIENTS WITH NO PREVIOUS VOLUNTARY COMPLAINT OF PRURITUS VULVAE

| | NUMBER | PERCENTAGE | COMPLAINED OF SYMPTOMS ON CLOSE QUESTIONING |
|---|--------|------------|---|
| <i>Candida albicans</i> | 20 | 10 | 10 |
| <i>Candida stellatoidea</i> | 38 | 16 | 15 |
| <i>Candida parakrusei</i> | 7 | 3.5 | 1 |
| <i>Candida Krusei</i> | 4 | 2 | 0 |
| <i>Candida tropicalis</i> | 2 | 1 | 0 |
| <i>Cryptococcus sp.</i> | 14 | 7 | 0 |
| <i>Saccharomyces sp.</i> | 2 | 1 | 0 |
| Total incidence of yeasts or yeastlike fungi from vulvas and vaginas | | | 43% |
| Total incidence of yeasts or yeastlike fungi from vagina | | | 33% |
| Number of symptomatic patients with a multiple infection with both trichomonads and fungi | | | 19 |

Present Report

The present report deals with a group of selected patients, both pregnant and nonpregnant, who sought medical advice because of pruritus vulvae and other symptoms referable to a mycotic vulvovaginal infection. Large numbers of records were reviewed carefully, and no patient is included with complicating diseases which could conceivably contribute to the symptoms.

In Table III are shown the fungi belonging to the genus *Candida* isolated from two hundred eighty of these patients. In this group there were one hundred eighty-nine nonpregnant patients and ninety-one pregnant patients. The ratio of white and Negro was two hundred fifty-one white and only twenty-nine Negro. These figures are somewhat misleading, as most of the patients were private patients and there would undoubtedly be more Negro patients in clinic practice.

TABLE III. SPECIES OF CANDIDA (MONILIA) ISOLATED FROM 280 PATIENTS WITH A CHIEF COMPLAINT OF PRURITUS VULVAE AND WITHOUT OTHER COMPLICATING FACTORS

| | NUMBER | PERCENTAGE |
|-----------------------------|--------|--------------------------|
| <i>Candida albicans</i> | 255 | 91.07 |
| <i>Candida stellatoidea</i> | 19 | 6.78 |
| <i>Candida parakrusei</i> | 5 | 1.07 |
| <i>Candida Krusei</i> | 1 | 0.36 |
| <i>Candida tropicalis</i> | 2 | 0.71 |
| White patients | 251 | Gynecologic patients 189 |
| Negro patients | 91 | Obstetric patients 91 |

The age incidence is interesting in that all of the patients were in the menstruating age with but three exceptions. Two patients were between 50 and 60 years of age, and one patient was over 60 years of age.

Discussion

Fungi belonging to the genus *Candida* are etiologic agents in a specific form of vulvovaginitis. Vulvovaginitis can be produced experimentally by the inoculation of normal vaginas with pure cultures of *Candida albicans*.

Although the disease is more frequently recognized, too much dependence has been put on classic findings at vaginal examination. Many patients do not show signs, and the diagnosis is not made because of the failure to use culture methods.

The commonest type of therapy used is 1 per cent aqueous gentian violet applied to the vulva, vagina, and cervix two or three times weekly. This, of course, cannot be done satisfactorily by the patient, is a messy form of treatment, soils the patient's clothing, and chemical reactions are not uncommon. In our experience the results obtained hardly justify its use. Other treatments in general use are carbosome, silver picrate insufflations, and suppositories and the iodides.

For the past two years we have been using a vaginal jelly with a bentonite base and calcium and sodium propionate as the active ingredients. A report now in press by Alter, Jones, and Carter²² gives the results of treatment, with follow-up cultures, on fifty-four patients. At the present time we have treated over one hundred patients with excellent results.

Some of the advantages of this form of therapy are: the jelly is prepared in tubes and patients are given an applicator which delivers a measured amount of jelly. The jelly is entirely innocuous, convenient to use, and does not stain the patient's clothing. Relief of pruritus and other symptoms in practically every instance is prompt. A cure was obtained after one series of treatments in 80 per cent of the nonpregnant patients and in 33 per cent of the pregnant patients. The criteria of cure are based on obtaining negative cultures. Even though cultural cures were not effected in many pregnant patients, symptomatic relief was obtained without fear of ill-effects.

Previous Related Study

In 1940, Carter, Jones, Thomas and Ross²¹ reported the results of cultures for fungi from the vulva and vagina of two hundred pregnant females. This earlier study was of an investigative nature. A mimeographed history sheet was used, and all patients were asked the same questions. No leading questions were asked. The only criteria for including the patient in the study were that the patient must be pregnant and have no previous voluntary complaint of symptoms referable to a vaginal mycotic infection. Since none of the patients had complained when symptoms were present, they were not unbearable from the patient's standpoint. This is shown further by the fact that if a positive culture were obtained, the patient was not informed, and only a small number required treatment during that pregnancy.

In Table II is shown the incidence of yeasts and yeastlike fungi isolated, and the number of patients who on close questioning had associated symptoms. Nineteen of the twenty-six symptomatic patients had a multiple infection with both trichomonads and fungi.

In considering Table II, several conclusions are possible: (1) The incidence of yeasts or yeastlike fungi on the vulva or in the vagina of the pregnant female is out of proportion to the symptomatology. This is particularly true of the clinic or Negro patient. (2) Compared to the high incidence, few require treatment. (3) Due to the lack of clear-cut symptoms and the high incidence of associated trichomonads, a study of this type is of only slight value in determining the most frequent vaginal pathogens. (4) The fungi isolated are of several genera and numerous species. (5) The number of strains of *Candida stellatoidea* isolated may be of some significance, but no definite conclusions regarding this new species is possible.

THE MANAGEMENT OF BREECH PRESENTATION*

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THE management of breech presentations is a controversial subject. It is of interest to most obstetricians and requires further study. We have analyzed 291 breech deliveries occurring in 6,476 consecutive deliveries in our private practice since September, 1928, an incidence of 4.49 per cent for breech deliveries. We have included all breech presentations occurring in single and multiple pregnancies when the baby weighed 1,814 Gm. (4 pounds) or more at birth. All pregnancies of twenty-eight weeks or more, and a few earlier pregnancies, were included by this standard.

As used in this discussion, private patients include all patients receiving prenatal care in our office, and patients referred to us as private patients during labor. Approximately one-third of our patients are referred to us because of various complications of pregnancy and labor. Our gross statistics include all babies who weighed 4 pounds at birth regardless of the condition of the baby and mother when we were first consulted. In two cases the fetus had died in utero before the onset of labor. Three mothers had eclampsia and were referred to us because of convulsions and hypertension.

Our patients have all been treated individually. An attempt has been made to determine the advisability of vaginal or abdominal delivery before the onset of labor whenever it was possible. We believe in the conservative treatment of patients with breech presentations. The onset of labor should be spontaneous whenever the patient's condition permits this procedure, and the membranes should be kept intact until delivery is imminent. Because of complications in many of our patients this plan could not be followed.

When the mother's condition remains good and the labor progresses normally without any indication of fetal distress, we let the hips of the baby deliver spontaneously, and then, under anesthesia, we guide the shoulders and head through the birth canal. In assisting a breech delivery, and whenever it is necessary to extract a baby presenting as a breech, we follow Potter's technique. Piper forceps are applied whenever the head cannot be delivered easily. The Celsus-Wiegand-Martin maneuver can be used to advantage in delivering the aftercoming head through the pelvic canal whenever assistance is indicated. In our opinion Mauriceau's maneuver for delivery of the aftercoming head is dangerous, and frequently causes injury to the baby. We do not use this maneuver.

*Read at the annual meeting of the South Atlantic Association of Obstetricians and Gynecologists, Savannah, Ga., Feb. 8, 1947.

The tendency to treat pruritus vulvae as a disease and not as a symptom results too often in the overtreated or incorrectly treated patient.

Conclusions

1. Two hundred eighty patients with mycotic vulvovaginitis and without other complicating diseases are reported.
2. *Candida albicans* was isolated and identified from 91.07 per cent of these patients.
3. Other species of *Candida* produce vulvovaginitis in the occasional patient.
4. The vaginal fungi, symptomatology, clinical findings, and treatment are discussed.

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Dieckman, in 1946, advised individual evaluation for each patient with a breech presentation. He states, "We do not believe in a routine prophylactic 'breaking up' of the breech and pulling down one or two legs, but we do use this procedure in selected patients where labor is unduly slow."

A review of the literature indicates that many obstetricians favor elective cesarean section for the patient with a breech presentation if she is an elderly primipara, and for the patient with a borderline pelvis if the size of the baby indicates cephalopelvic disproportion.

Siegel and McNally, in 1939, advocated external version in breech presentations to reduce fetal mortality in primary breech presentations. They reported 68 cases in which attempts had been made by external version to change breech presentations to vertex presentations. In 55 patients the versions were successful.

Ryder, in 1943, advocated external version for most breech presentations and reported an incidence of breech presentations at time of birth in 2.6 per cent of his private deliveries. His rate of 2.6 per cent is much lower than ours, which is 4.49 per cent for all breech deliveries. One's statistics may be easily influenced by the per cent of referred patients with complications, and this may be an important factor in our incidence of breech deliveries. Moore and Steptoe, in 1942, reported from The Johns Hopkins Hospital an incidence of breech presentations of 2.8 per cent of all births. If routine attempts to convert breech presentations to vertex presentations by external version are successful, fetal mortality rates can be lowered by this procedure. In our cases external version was rarely attempted. The figures so far presented for this procedure are not convincing.

TABLE I.

| | |
|---|-----|
| Total number patients (mothers) | 290 |
| Total number patients (babies) | 291 |
| Total number twin pregnancies (one breech) | 18 |
| Total number twin pregnancies (both breech) | 1 |
| Twin pregnancies, first baby breech | 6 |
| Twin pregnancies, second baby breech | 12 |

All babies in this report weighed 1,814 Gm. (4 pounds) or more.

Table I shows the number of mothers and babies in this report. Twin pregnancies increase fetal mortality, but we have included them.

As shown in Table II, there were almost twice as many primiparas as multiparas in the cases we are reporting. This may tend to increase our fetal mortality rate.

TABLE II. DURATION OF PREGNANCY

| | 23-32 WEEKS | 32-38 WEEKS | 38-40 WEEKS | TOTAL |
|------------|-------------|-------------|-------------|-------|
| Primiparas | 2 | 22 | 168 | 192 |
| Multiparas | 1 | 16 | 81 | 98 |
| Total | 3 | 38 | 249 | 290 |
| Per cent | 1.03 | 13.05 | 85.56 | |

TABLE III. TYPE BREECH PRESENTATION

| | PRIMIPARAS | MULTIPARAS | TOTAL | PER CENT |
|-----------------|------------|------------|-------|----------|
| Frank breech | 147 | 69 | 216 | 74.22 |
| Complete breech | 32 | 22 | 54 | 18.55 |
| Footling breech | 13 | 8 | 21 | 7.21 |
| Total | 192 | 99 | 291 | 100 |

In our cases episiotomy was performed 197 times in 236 vaginal deliveries, an incidence of 83 per cent. This procedure reduces trauma to both the mother and baby. We think the frequent use of episiotomy has reduced both our fetal mortality and traumatic injuries to the babies. Episiotomy necessitates anesthesia, and it can be done just before the extraction of the baby is started. No third degree laceration occurred in any case in this series.

Analgesia was given to all patients in this study except those delivered by elective cesarean section and some of those with uterine inertia. As used by us, analgesia usually includes hyoscine, one two-hundredth of a grain, and pantopon, one-sixth of a grain, also nembutal, one and one-half to three grain doses, with a total of not more than nine grains of nembutal in a prolonged labor, and a smaller total for short labors.

Irving and Goethals, in 1926, advocated shortening the second stage of labor in breech delivery and emphasized the importance of deep anesthesia for the patient. During the twenty-one years since this original publication, Goethals has contributed several other papers to the literature on this subject. He has obtained excellent results in breech deliveries by the extraction of the baby after the cervix is fully dilated. He still advocates deep anesthesia for the extraction, and emphasizes the danger of extended arms and the difficulty one often encounters with the aftercoming head even when the body delivers spontaneously. If the patient is awake when difficulty is encountered in delivering the shoulders and head, valuable time is lost while she is being anesthetized.

Hansen, in 1940, reported one hundred² twenty-six breech deliveries occurring in 1882 consecutive private deliveries. After correcting for premature and abnormal babies his mortality rate for stillbirths and neonatal deaths was 0.8 per cent. Hansen stated, "Our method of treatment is conservative. By conservative treatment we mean giving supportive treatment to the mother with no interference unless labor is obstructed, progress ceases, or complications arise endangering the life of the mother, baby, or both."

Milton Potter, in 1945, advocated cesarean section for breech presentations in borderline pelves, and particularly in primiparas. For vaginal deliveries he favors breech extraction, under deep anesthesia, after the cervix is completely dilated and the lower segment of the uterus is well effaced.

In a recent publication Guyer and Heaton report that at Bellevue Hospital the routine management of breech delivery vaginally is to allow spontaneous delivery of the baby until the umbilicus presents, after which assistance is given for the shoulders and head.

Potter, Bill, and many others have stressed the importance of full dilatation and effacement of the cervix for a successful vaginal delivery of a breech presentation, even in a normal pelvis. Again we emphasize the fact that an incompletely dilated cervix will often permit delivery of the baby's body, but it will make delivery of the shoulders difficult and it predisposes to extension of the arms. In these cases the cervix often contracts around the baby's neck, retarding delivery of the fetal shoulders and head, and causing unnecessary trauma to both the mother and baby. This often results in permanent injury or death to the fetus. When the mother and baby are in good condition, a short time in the second stage of labor, to reduce the irritability or contractility of the cervix, often facilitates the delivery of the shoulders and head. This should be remembered whenever extraction of a breech presentation is undertaken as a necessary or optional procedure.

TABLE VIII. VAGINAL AND ABDOMINAL DELIVERY

| | | |
|-------------------------------|-------------|------------|
| Delivered vaginally | 235 mothers | 236 babies |
| Delivered by cesarean section | 55 mothers | 55 babies |

The average age of patients delivered by cesarean section was 28.8 years.

TABLE IX. CESAREAN SECTION INDICATIONS

| | |
|--|----|
| Generally contracted pelvis | 30 |
| Flat pelvis | 11 |
| Funnel pelvis | 3 |
| Cephalopelvic disproportion | 2 |
| Former extensive vaginal plastic operation | 1 |
| Borderline pelvis, irregular fetal heart | 1 |
| Former cesarean section, uterus didelphys | 1 |
| Former cesarean section, toxemia | 1 |
| Double vagina and cervix, prolapsed cord | 1 |
| Uterine inertia | 2 |
| Cervical stenosis | 1 |
| Toxemia, eclampsia | 1 |
| Total | 55 |

TABLE X. FETAL MORTALITY

| | TOTAL NUMBER | PER CENT |
|---------------------------------|--------------|----------|
| <i>Uncorrected</i> | | |
| Stillbirths | 5 | 1.71 |
| Neonatal deaths | 11 | 3.78 |
| Stillbirths and neonatal deaths | 16 | 5.49 |
| <i>Corrected</i> | | |
| Stillbirths | 1 | 0.30 |
| Neonatal deaths | 7 | 2.40 |
| Stillbirths and neonatal deaths | 8 | 2.70 |

TABLE XI. STILLBIRTHS AND NEONATAL DEATHS

| | NUMBER |
|--|--------|
| <i>Stillbirths</i> | |
| Hydrocephalus (craniotomy) | 1 |
| Meningocele | 1 |
| Erythroblastosis fetalis | 1 |
| Antepartum death (cause undetermined) | 1 |
| Intrapartum death (cause undetermined) | 1 |
| <i>Newborn Deaths</i> | |
| Spina bifida | 1 |
| Multiple deformities | 2 |
| Congenital heart | 1 |
| Atelectasis | 4 |
| Cause undetermined | 2 |
| Maternal toxemia | 1 |

Tables VIII and IX show the incidence of cesarean section and the indications, which are self-explanatory. For those who think the cesarean section rate too high we have two comments. One cesarean section for uterine inertia resulted in a stillborn apparently normally developed baby, and the operation should have been done earlier. This was the only stillborn baby in the group of patients delivered by cesarean section, and no newborn deaths occurred in this group. One other patient, a primipara 40 years old, was delivered by breech extraction and the baby died. She should have been delivered by elective cesarean section.

Table X shows the total uncorrected and corrected stillbirths and newborn deaths within three weeks after delivery for all babies weighing 1,814 Gm. (4 pounds) or more in 291 breech presentations.

TABLE IV. ONSET OF LABOR

| | NO. PATIENTS | PER CENT |
|--|--------------|----------|
| Spontaneous | 159 | 54.64 |
| Medical induction | 33 | 11.34 |
| Medical induction and amniotomy | 46 | 15.80 |
| Voorhees bag | 3 | 1.03 |
| Premature rupture of membranes (spontaneous) | 66 | 22.68 |

Prolapse of the cord did not occur in any case with artificial rupture of the membranes.

TABLE V. TYPE OF DELIVERY

| | PRIMIPARAS | MULTIPARAS | TOTAL |
|--------------------------------|------------|------------|-------|
| Spontaneous | 30 | 28 | 58 |
| Breech extraction | 85 | 51 | 136 |
| Breech converted and extracted | 35 | 7 | 42 |
| Forceps to aftercoming head | 73 | 17 | 90 |
| Cesarean section | 42 | 13 | 55 |

TABLE VI. AVERAGE DURATION OF LABOR (VAGINAL DELIVERIES)

| | FIRST STAGE | | SECOND STAGE | |
|------------|-------------|---------|--------------|---------|
| | HOURS | MINUTES | HOURS | MINUTES |
| Primiparas | 9 | 36 | 1 | 32 |
| Multiparas | 8 | 6 | 0 | 42 |

TABLE VII. COMPLICATIONS

| | PATIENTS |
|----------------------------------|----------|
| Prolapse of cord | 10 |
| Premature separation of placenta | 5 |
| Placenta previa | 0 |
| Polyhydramnios | 3 |
| Toxemia (preeclampsia) | 33 |
| Toxemia (eclampsia) | 3 |
| Postpartum hemorrhage | 11 |

Labor was induced in 28 per cent of our patients. Most of the inductions were done because of premature rupture of the membranes or maternal toxemia. It is interesting to note that prolapse of the umbilical cord did not occur in any case after artificial rupture of the membranes. We never intentionally rupture the membranes until the presenting part is well engaged in the pelvis.

As shown in Table V, the percentage of spontaneous deliveries was low, and the incidence of cesarean sections was high. These operations were usually indicated because of some type of cephalopelvic disproportion, but we do deliver by elective cesarean section many patients with breech presentations who would be given a trial labor with a vertex presentation.

The average duration of labor in both primiparas and multiparas was shorter in our cases than the average given in most textbooks on obstetrics. The longest labor in this study in a primipara was fifty-three hours, and the longest in a multipara was seventy-six hours.

The complications are shown in Table VII. There were ten patients in whom the umbilical cord prolapsed, but no fetal death occurred in this group. We attribute this to the fact that the fetal heart sounds are watched closely and recorded frequently when the breech presents. We usually stay near the breech cases when labor is active. Five patients developed premature separation of the placenta, but all had living babies. Five patients were transfused. In six patients the uterus was packed with gauze to control bleeding.

September, 1928, have been presented. In this series there were five stillbirths and eleven newborn deaths, an uncorrected fetal mortality of 5.46 per cent. There was no maternal mortality in this series of cases.

After deducting for babies with congenital deformities incompatible with life, and two babies who died in utero before the onset of labor, the corrected stillborn and newborn death rate is 2.70 per cent for all babies weighing 4 pounds or more. |

When the baby presents as a breech in an elderly primipara, or when a patient has a borderline pelvis and a large baby, delivery by cesarean section should be carefully considered and resorted to frequently.

There is a distinct difference between a fully dilated cervix and a fully dilated and paralyzed cervix. In breech deliveries the former frequently contracts around the baby's shoulders or neck and causes difficulty in delivering the shoulders and aftercoming head. When the cervix is fully dilated, retracted, and paralyzed it rarely interferes with the delivery of the shoulders and aftercoming head. Overextension of the fetal head in the delivery of a baby presenting as a breech is dangerous and often results in injury or death to the baby.

After the cervix is completely dilated and effaced, breech extraction under anesthesia may lower fetal mortality for trained and experienced obstetricians.

Episiotomy before delivery of breech presentations probably reduces trauma to the baby and mother and decreases fetal mortality.

Every woman in labor with the breech presenting should be watched closely and the fetal heart rate studied carefully for indications of fetal distress.

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The corrected stillborn and newborn death rate of 2.70 per cent could be lowered by omitting two fetal deaths occurring in babies whose mothers had severe toxemias. One of these fetal deaths is recorded under atelectasis. Four of the five stillbirths would have been lost regardless of the presentation, and four of the eleven neonatal deaths were unavoidable because of congenital defects.

TABLE XII. CORRECTED FETAL MORTALITY IN PRIMIPARAS AND MULTIPARAS

| | PRIMIPARAS | | | MULTIPARAS | | |
|--------------------------------|----------------------|--------------------|-------------|----------------------|--------------------|-------------|
| | NUMBER DELIVERIES | FETAL MORTALITY | PER CENT | NUMBER DELIVERIES | FETAL MORTALITY | PER CENT |
| Spontaneous | 30 | 0 | 0 | 28 | 0 | 0 |
| Breech extraction | 85 | 4 | 4.69 | 51 | 1 | 1.96 |
| Breech converted and extracted | 35 | 1 | 2.85 | 7 | 1 | 14.28 |
| Forceps to aftercoming head | 73 | 3 | 4.10 | 17 | 0 | 0 |
| Cesarean section | 42 | 1 | 2.35 | 13 | 0 | 0 |
| Total (omitting forceps) | 192 | 6 | 3.11 | 99 | 2 | 2.02 |

Our series of cases is too small to be of value when broken down as in Table XII. One might conclude from the figures on conversion and breech extraction that this is a dangerous procedure, but one of the two babies lost had multiple congenital deformities. An additional factor to consider is that breaking up the breech and then extracting it is resorted to in the most difficult cases. The same applies to the use of Piper forceps to the aftercoming head.

TABLE XIII. CORRECTED FETAL MORTALITY RATES OF VARIOUS AUTHORS
(Adapted from Guyer and Heaton)

| AUTHOR | YEAR OF PUBLICATION | FETAL MORTALITY RATE, PERCENTAGE |
|-------------------------|------------------------|-------------------------------------|
| Caldwell and Studdiford | 1929 | 11.11 |
| Cannell and Dodek | 1934 | 6.75 |
| Macafee and McClure | 1937 | 6.10 |
| Mohler | 1938 | 5.50 |
| Siegel and McNally | 1939 | 12.10 |
| Patton and Mussey | 1940 | 3.77 |
| Hawker and Soule | 1940 | 4.81 |
| Goethals | 1940 | 7.40 |
| Hansen | 1941 | 0.80 |
| Waters | 1942 | 11.20 |
| Tompkins | 1943 | 2.70 |
| Moore and Steptoe | 1943 | 12.80 |
| Guyer and Heaton | 1946 | 4.50 |
| Dieckman | 1946 | 1.70 |
| Ware, Winn, Schelin | 1947 | 2.70 |

Table XIII is the original table of Guyer and Heaton brought up to date by the addition of the last three reports appearing in 1946 and 1947. This table is interesting, but of little value in comparing statistics because of the difference in the standards used in estimating and correcting fetal mortality. Babies weighing 4 pounds or more should be separated from those weighing less than 4 pounds as the chance for survival of babies born alive but weighing less than 4 pounds is very poor. We should use both gross and corrected rates for stillbirths and neonatal deaths.

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Summary and Conclusions

Two hundred ninety-one cases of primary breech presentation, delivered as breech presentations occurring in 6,476 consecutive private deliveries since

available medical attendants in smaller communities are other reasons why women seek obstetric care in urban centers. In all probability, the problem will increase rather than decrease, unless a successful answer lies in the establishment of hospitals in smaller towns as proposed by our government agencies.

In our city (Atlanta), many patients living within a radius of 25 to 250 miles are registered for care in the maternity section of the hospitals at the time of delivery. These women truly present a serious problem for adequate and satisfactory obstetric management. Inasmuch as the problem apparently is increasing, it is felt that there is need for the adoption of some systematized plan of management for the nonresident patient at the time of confinement.

Experience has convinced us that no single expedient is available to all cases. Too many factors must be considered in determining the course to be followed in the management of labor in this group of women. In considering a course of management in nonresident patients with normal pregnancies, three choices are available:

1. *Awaiting the spontaneous onset of labor at home.*—For patients living within a radius of 25 to 50 miles of the hospital, especially primigravidas, the attendant assumes that ample time will be available for transportation to the hospital after the spontaneous onset of labor in all but exceptional cases. This is based upon the fact that several hours usually elapse from the onset of ten- to fifteen-minute pains, to three- to four-minute pains when dilatation begins and the patient experiences considerable discomfort. For multiparas, especially those with a history of rapid previous labors, this plan is hazardous. Too often the latter are deprived of the comfort of analgesic and amnesic medication during labor, in addition to being subjected to both maternal and fetal danger by precipitate delivery en route to the hospital. It is our belief that this plan of management is not applicable with a great degree of safety to patients who reside beyond a radius of 50 miles of the hospital, unless a barbiturate is administered before leaving home.

Also, because of the ever present apprehension concerning arrival at the hospital in time for delivery, the incidence of "false labor" is greater among women who spontaneously enter labor at home. This type of patient not only demands attention needed by other more actively laboring patients, but invites meddlesome measures aimed at stimulation of labor and is often the victim of prolonged or difficult labor initiated by request or thought advisable by the attendant because of the distance between her home and the hospital.

2. *Establishment of residence in the vicinity of the hospital within a short time of the expected date of confinement.*—This may involve considerable expense, cause accompanying members of the family to remain away from their respective duties, or disturb the mental comfort of the woman as a result of separation from her family, especially if she has children at home. Too, pregnant women offer problems of individual care concerning their diet and recreation in both homes and hotels. Also, with the spontaneous onset of labor, transportation must be available. This plan is nearer ideal in cases where the patient can be placed in the home of relatives. One advantage of this method of handling lies in the possibility of attempting medical induction of labor one or more times at or near the expected date of confinement.

3. *Admission to the hospital for elective induction of labor.*—This plan of management, both for the convenience of the patient and attendant, has met with considerable favor during the past decade. That it does not prove to be the answer for all cases is borne out by statistics later in this paper.

THE PROBLEM OF DELIVERY OF THE NONRESIDENT PATIENT*

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IN LARGE obstetric services, both private and clinic, the management of labor in women who live at a great distance from the hospital in which they plan confinement is still a problem for the attendant. Especially was this true during the years of the recent war, at which time many smaller communities were deprived of an adequate number of physicians. The result was an influx of obstetric patients into urban centers. The number and variations of techniques in the management of such cases in use today offer proof that none has proved exceptionally successful for this type of patient. A review of the literature reveals that, so far, no routine systematic plan of management applicable to all such cases has been recommended. So far, this type of case has either been considered individually, or action has been taken based upon the requests and dictates of the woman as she approaches term with considerable apprehension for safety regarding the course of labor.

All too frequently one encounters a frantic patient, at or near term of a carefully supervised normal pregnancy, in an unexpected precipitous type of labor living at a remote distance from the attendant and hospital of her choice. On the other hand, recall the nonresident patient whose labor was complicated by prolonged dystocia secondary to uterine inertia and terminated by difficult operative interference after labor was electively induced rather than permit the patient to travel a long distance following the spontaneous onset of labor.

A survey of admissions to the maternity section of large urban hospitals convincingly reveals that the percentage of patients from rural districts and surrounding towns is on the increase.

Several factors influence women to decide upon delivery in urban hospitals at a remote distance from their homes. For the majority, the desire that labor be conducted under amnesic and analgesic medication in the hands of attendants specializing in obstetrics is the factor responsible for hospitalization away from home. For others, the safety and comfort of hospitalization, not available in smaller towns or communities, are the factors. Other women desire the services of an attendant specializing in obstetrics. Especially is this true of those who during a previous pregnancy encountered complications or difficulties. The latter always are difficult patients, inasmuch as apprehension regarding a successful outcome during labor is ever present. The desire to return to the obstetrician who successfully attended a previous pregnancy, better economic conditions, improved transportation facilities, and the decrease in the number of

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labor is offered, the obstetrician must rely upon some method of determining the most favorable time for the induction of labor which statistically offers the best results.

It is regrettable that statistics fail to answer some of our most perplexing questions regarding the safe time for the induction of labor. For example, on the part of the mother: is pregnancy at term? is the latent period to be dangerously prolonged? is the uterus capable of sufficient power? is the cervix to offer unexpected resistance. is infection a factor? and finally, is there increased danger of hemorrhages, trauma, or will difficult operative procedures be necessary? On the part of the fetus: is it mature? is there danger of prolapse of the cord? is deflection likely to be produced? is placental trauma possible? and finally, is it capable of withstanding trauma in the face of possible operative interference aimed at delivery? In short, unless the attendant is willing to assume that he has the answer for the preceding questions he must assume the moral and legal responsibilities associated with the potential dangers surrounding the initiation of a process which nature so far has not assumed.

Since it has been thought, and with good reason, that the possibility of spontaneous onset of labor at a place remote from that of planned confinement constitutes an additional hazard to the parturient, it seems that the adoption of some plan of management, study of procedures, and analysis of statistics concerning maternal and fetal results in this group of women would be of value.

We are convinced, in the handling of the nonresident patient, that if there is any single criterion which enables one to feel assured that the patient is near term or due, it is the change in the lower uterine segment and cervix which occurs as the majority of women prepare for labor. Especially is the change of value if it has been observed by palpation over a period of days or weeks by the same examiner.

Procedure

It is our purpose to outline a plan of management during late pregnancy, which not only will enable the mother to receive the full benefit of analgesia and amnesia and safety during labor, but which will also enable the fetus to reach a stage of safe maturity. Further, it is desired to emphasize a safe approach and method of inducing labor and, particularly, the conditions necessary in determining the contraindications to induction or postponement until labor can safely be initiated. Especially it is desired to emphasize the changes which occur in the cervix and time interval following a failure at induction which enable one to determine the safe time for a repeated attempt at induction in this group of women.

We have learned to attach great importance to the condition of the cervix—its length, consistency, degree of patency, location in the vagina, and relation to the overlying presenting part—in drawing conclusions regarding the proper time to initiate labor. Especially important are the changes observed by repeated pelvic examination during the terminal month of pregnancy or following a failure of induction by conservative measures. Too, we are impressed with the value and safety of office vaginal examination at the end of thirty-six and

It is far from the ideal form of management for the nonresident patient inasmuch as the success of induction, type of labor, and condition and size of the fetus cannot definitely be predicted at the time of attempt to initiate labor. Too often, in addition to maternal complications, the service of a nursery is overtaxed as the result of an excessive number of premature infants delivered of women thought to be mature at the time labor was induced.

Reviewing the literature, one finds that the indications for induction of labor have rapidly increased during the past decade. Among these appear "patients who live at distance from the hospital." One is not only impressed by the advantages of elective induction at or near term but is also made conscious of the dangers of the procedure in such a review.

Morton¹ reports induction of labor by means of artificial rupture of the membranes, castor oil and quinine and intranasal pituitrin. Guttmacher,² in 1931, and Slemons,³ in 1932, reported on induction of labor by means of artificial rupture of the membranes, but stressed that the latent period and duration of labor are shorter whenever the cervix is naturally effaced and partially dilated at the time the membranes are ruptured for induction of labor. Stern,⁴ Plass,⁵ and Mathieu and Holman⁶ all report a low morbidity, mortality, and excellent results obtained by induction. However, as Roblee⁷ has pointed out, it must be remembered that their material was selected from abundance and that their skill, judgment, and environment were of the best.

On the other hand, in 1940, Cornell⁸ called attention to the dangers, both physical and legal, which are always present when one attempts to interfere with the normal processes of pregnancy and labor. He emphasized that it is not possible to predict when a patient is at term by the size of the baby physically or by x-ray, by the date of the period, or from quickening. He also pointed out the dangers of prolonged labor, increased fetal mortality, infection of the placenta, increased hemorrhage, prolapse of the cord, and increased morbidity associated with elective induction of labor.

Roblee,⁷ in 1946, after reviewing 500 cases of induced labor, concluded that the character and results of induced labor approach that of normal spontaneous labor only when it precedes by 48 or less hours the time when spontaneous labor would have occurred anyway. Other authors likewise point out the minor dangers associated with induction at term.

At present we are without an answer to predict the time or explain the cause of the spontaneous onset of labor. Reynolds⁹ is of the opinion that the cause of onset of labor is tied up with a change in the estrogen-pituitary-progestin balance, brought about by uterine distention. The most promising answer comes from Lyon¹⁰ in his search for the etiologic factors concerned in the time of onset of spontaneous labor. Using the glucuronic acid method he found that the sodium pregnanediol glucuronidate curve of excretion in the urine decreased preceding the onset of labor at term, post mature, and in premature groups in a parallel manner. There was a positive relationship between a sudden drop in conjugated pregnanediol and the onset of labor.

As stated by Roblee,⁷ with this new knowledge available a different interpretation may be placed on the subject of induced labor. Certainly it offers an optimistic promise of valuable information to clinical obstetrics.

Inasmuch as the causative factors of the spontaneous onset of labor are still unknown, one must exercise caution in instituting any procedure aimed at the initiation of the process of labor. Too often, the clinical obstetrician must, in cases of dystocia due to uterine inertia, witness a miserable failure on the part of nature to complete a so-called normal process. Until a more satisfactory explanation of the causative factors involved in the onset of spontaneous

less, it is valueless, and in some instances apparently accelerates labor. Especially is this true if the membranes have ruptured. It is not safe, even with barbiturate, for a multipara, living one to two hours' drive distant, to attempt to reach the hospital after the membranes have ruptured.

For those who present evidence of impending or short labors and live beyond a distance of 50 miles of the hospital, it is thought advisable to have them establish residence near, or enter the hospital for an attempt at elective induction of labor.

For those fortunate in securing residence near the hospital, pregnancy is permitted to continue to term and await spontaneous onset of labor, or medical induction is attempted at a later date. It is our custom to permit such patients to continue pregnancy until the calculated date of confinement before attempting medical induction. The simple method of administering two ounces of castor oil followed by a hot soapy enema after thorough bowel evacuation has proved highly satisfactory for these cases. We are not convinced that the addition of quinine to the procedure has additional value. Too, as a rule, if castor oil is ineffective in producing labor, the pregnancy will advance five or more days before the spontaneous onset of labor. Therefore, it is not advisable to repeat the procedure short of that time.

For patients living a distance of more than 50 miles from the hospital the course of management should be directed differently, if unable to establish residence in or nearer the hospital to await spontaneous labor. For this group of women it is felt that a slightly increased degree of responsibility must be assumed on the part of the attendant and the patient be admitted to the hospital for a trial induction of labor. If, after admission, vaginal examination reveals that the cervix still has some length or the rim is thick, not softened and not dilated more than 1 to 2 centimeters, it is best to avoid attempted induction and select another course, even if the patient is at or past the expected date of confinement. Often this decision will save the patient a prolonged inertia type of labor and the usual complicated operative procedures necessary for its termination.

In discussing elective induction of labor in women presumed to be at or near term, it is necessary that the parity and rapidity of previous labors be considered.

In the nulliparous woman possessing a doubtful cervix, it has been our custom to administer 2 ounces of castor oil following complete preparation for labor, after admission into the hospital. This is followed by a hot soapy enema after the bowels are evacuated. In many cases this simple procedure has been effective in producing labor. At the end of eight to ten hours, if labor is not established, pitocin, administered as intranasal drops every fifteen minutes for twelve doses, is started. Following the intranasal medication a vaginal examination is done and the membranes gently stripped by the examining finger, for 1 to 2 centimeters around the internal os. If labor has not started within twenty-four hours following these procedures, the patient is permitted to leave the hospital and establish residence in the vicinity of the hospital, but not return home.

On the other hand, in nulliparous patients with very thin, soft, elastic, and partially dilated cervices, the membranes are stripped and ruptured following the series of twelve doses of intranasal Pitocin. In some cases, it is necessary to repeat the Pitocin drops in series of 10 to 12 doses at 4 hour intervals after the membranes are ruptured before labor is well established.

In multiparous women, due to the usual high station of the head before labor is well under way, care should be exercised in promiscuously rupturing the membranes artificially in an effort to initiate labor. In this type of patient, it is best to administer castor oil, use Pitocin drops and adhere to a policy of stripping the membranes, reserving artificial rupture of the sac until the head

thirty-eight weeks of pregnancy. On several occasions the results of an office rectal examination were not confirmed by hospital vaginal study following admission of the patient for induction. Several of such cases were dismissed with instructions to return at a later date for another sterile vaginal examination in the hospital. Too, it is important to point out that marked changes can occur in the cervix near the end of pregnancy within a period of only a few days, thereby converting an unfavorable to an ideal structure for inducing labor. These changes were especially outstanding after periods of five to fourteen days in women dismissed following unsuccessful attempts at induction by castor oil, intranasal pituitary drops, and stripping of the membranes.

In selecting the time for induction, in addition to the condition of the cervix, one must consider the parity, the necessary distance of travel if labor should start at home, the duration of previous labors, the size of the fetus, and the estimated date of confinement. Too much emphasis cannot be placed upon the menstrual history with any degree of accuracy. For example, one would suspect that labor would occur early if the last menstrual flow preceding amenorrhea was shorter than usual. In our experience this suspicion has not been confirmed.

Since we have learned to attach important significance to the condition of the cervix in determining the time for induction, or onset and duration of labor, it has been our custom to make a sterile vaginal examination at the office at the end of thirty-six weeks in these women. The findings are carefully recorded for comparison with a subsequent vaginal or rectal palpation at the end of two weeks. In any case, if vaginal examination at the end of 36 weeks reveals that the cervix still has some length or that the rim is thick, firm, not universally softened, not dilated more than 2 centimeters, and accompanied by a high station of the presenting part, the patient is permitted to return to her home for seven to ten days rather than attempt induction of labor. As a rule, this examination will enable one to decide if the patient is to be permitted to enter spontaneous labor at home, is to establish residence near the hospital, or is to be admitted to the hospital at a fixed date for a trial at induction of labor. In other words, in addition to evaluating the condition of the cervix, the examiner must be able to anticipate the rapidity with which subsequent changes in the cervix favorable for labor will occur.

It is felt that the management of patients living within a 50 mile radius of the hospital should be different from that of patients who live beyond that distance.

In the former, especially those capable of short labor, it is our custom to have the woman secure 3 grains of Nembutal during the latter weeks of pregnancy. She is instructed to take the capsules, after the onset of labor, before leaving home for the hospital. This medication not only allays apprehension and increases the interval between contractions, but also has a mild analgesic effect and serves as a preliminary medication to other analgesic and amnesic drugs to be administered after admission into the hospital. It has been found that, in order to be effective, the barbiturate should be used when uterine contractions are occurring at eight- to ten-minute intervals, otherwise it is of little or no value. If withheld until contractions are at intervals of five minutes or

TABLE II. SEVENTY-SIX PATIENTS INSTRUCTED TO AWAIT ONSET OF LABOR AT HOME
(Average duration of labor 14 hours; 48 primigravidas and 28 multigravidas)

| | NUMBER | PER CENT |
|---|--------|----------|
| Admitted to hospital in ample time for delivery | 76 | 100.0 |
| Ample time for satisfactory analgesia and amnesia | 68 | 89.4 |
| "False labor," returned later in true labor | 4 | 5.2 |
| Barbiturate, preceding transportation | 40 | 52.6 |
| effective | 24 | 60.0 |
| not effective (membranes ruptured in 6) | 16 | 40.0 |
| Mortality (1 fetal monster) | 1 | 1.3 |
| Distance of travel after onset of labor, 30 to 83 miles | | |

(48 primiparas, 28 multiparas) was, in round numbers, fourteen hours. In 68 cases (89.4 per cent), the patients were admitted in ample time to secure satisfactory analgesia and amnesia before delivery. In the remaining 8 (10.6 per cent), the pain relief was not adequate because of advanced labor at the time of admission. Six of the latter were multiparas. In four instances the labor proved to be false. All four returned to their homes following a stay of a few hours in the hospital and all later returned and delivered after spontaneous onset of labor. Of 40 cases receiving 3 grains of nembutal before admission, 24 (60.0 per cent) noted an appreciable effect upon uterine contractions. All of these received the medication before the contractions were less than eight minutes apart. In 16 (40.0 per cent), six of whom had had the membranes rupture prematurely, no effect was apparent. In all of 16 the charts revealed the presence of contractions at intervals of less than eight minutes at the time the medication was used. In this group there was one fetal mortality, a 34-week monstrosity, weight 4 pounds, 8 ounces, which died within thirty minutes after birth.

TABLE III. THIRTY-FIVE PATIENTS ADVISED TO ESTABLISH RESIDENCE NEARER HOSPITAL
(Average duration of labor nine hours; 17 primigravidas and 18 multigravidas)

| | NUMBER | PER CENT |
|---|--------|----------|
| Satisfactory analgesia and amnesia | 35 | 100.0 |
| Spontaneous onset of labor within 8 days | 13 | 37.1 |
| Induced with castor oil (toxemia 2, overdue 6) | 10 | 28.5 |
| Morbidity and mortality | 0 | --- |
| Distance of permanent home from hospital (50-200 miles) | | |

TABLE IV. SEVENTY-SIX PATIENTS ADMITTED TO HOSPITAL FOR INDUCTION OF LABOR
(Average duration of labor eleven hours; 24 primigravidas and 52 multigravidas)

| | NUMBER | PER CENT |
|--|--------|----------|
| Correct prediction of cervical changes favorable to induction | 69 | 90.7 |
| Induction not attempted, cervical changes not as predicted | 1 | 1.3 |
| Induction, attempted | 75 | 98.6 |
| success | 69 | 92.0 |
| failure | 6 | 8.0 |
| Deliveries, pelvic | 74 | 98.0 |
| cesarean | 1 | 2.0 |
| Mortality, fetal (1 prepartum, 1 polyhydramnios 4 pounds, 3 ounces) | 2 | 2.6 |
| Morbidity, maternal | 3 | 4.0 |

Table III is an analysis of 35 cases in which, because of expected short labor or great distance of the home from the hospital, it was advised that residence be established nearer the hospital within a period of seven to thirty days of the time of delivery. Seventeen were primigravidas and 18 were multiparous

is lower and labor is well established. It is true that actual rupture of the sac insures labor and is more spectacular in result, yet, the ever present possibility of a prolapse of the cord in multiparas must constantly be kept in mind.

Naturally, if, at any stage of the program, labor is in evidence, one should omit subsequent steps and permit labor to progress in a normal manner. It has been our experience that once labor seems initiated with castor oil, time should be permitted for it to proceed to forceful contractions before additional stimulation is begun. In the presence of subsiding contractions, supplementary and persistent stimulation by pituitary products, intranasally or subcutaneously, is less likely to be effective and often produces a prolonged course in a patient who otherwise would have gone several days longer before the onset of labor. In other words, the uterus was not ready for labor.

TABLE I. RESULTS OF MANAGEMENT OF 187 NONRESIDENT PATIENTS
(Determined by Pelvic Examination Late in Pregnancy)

| | |
|--|-----------------------------------|
| Distance | 30 to 250 miles |
| Parity { Primigravidas | 89 |
| { Multigravidas | 98 |
| Instructed to await onset of labor at home | 76 |
| Advised to establish residence nearer hospital | 35 |
| Admitted to hospital for induction of labor | 76 |
| Time of pelvic examination | 40 to 0 days before delivery |
| Maternal mortality 0 | Infant mortality 3 (1.6 per cent) |

That the nonresident patient can have hospital delivery, secure the service of an obstetric specialist, receive analgesic and amnesic labor and successful delivery of a mature infant, may be seen from an analysis of 187 such cases in which management was determined by vaginal and rectal examinations made late in pregnancy. Table I shows an analysis of the methods of management of this group of women. The deliveries occurred between 1941 and 1946 and in the majority of cases the examinations and deliveries were conducted by one of us (R.A.B.) during military service of the co-authors.

The distance between the permanent home and the hospital varied between 30 and 250 miles. Without doubt war conditions were responsible for a number of the cases, inasmuch as many women preferred to remain at training sites with their husbands as long as possible before delivery. Too, the inadequate medical service resulting from military demands for the more active physicians in smaller towns and cities caused many women to seek obstetric care at a distance from their homes. However, for the majority, the demand for analgesia and amnesia in the hands of an obstetric specialist was the factor. In the group were 89 primigravidas and 98 multigravidas.

In regard to management, following evaluation of the cervical findings by pelvic examination in the office, 76 were instructed that it would be safe to enter spontaneous labor at home; 35 were advised to establish residence nearer the hospital inasmuch as short labor was expected, and 76 were admitted to the hospital for induction of labor because it was considered possible that the necessary distance of travel or danger of short labor would be hazardous. The pelvic examinations, as previously described, were done between 40 days before and the estimated date of labor. The maternal mortality was zero, the fetal mortality 3 (1.6 per cent).

Table II shows an analysis of the results in 76 women living between 30 and 83 miles of the hospital who were told that it would be safe to travel to the hospital following spontaneous onset of labor. All 76 reached the hospital in time for complete preparation and delivery. No precipitate delivery occurred, but one woman, a multipara, traveled 30 miles and was delivered thirty-five minutes after admission to the hospital. The average duration of labor

was considered unwise to take additional steps aimed at stimulation, was dismissed and re-entered the hospital four days later in spontaneous labor. In 11 cases (14.7 per cent), in addition to preliminary oil and intranasal drops, the membranes were stripped but not ruptured. Six (54.5 per cent) of these were successful, but in 5 (45.5 per cent) the measure failed and the women were dismissed from the hospital twenty-four hours later and instructed to remain near the hospital. Four were subsequently admitted to the hospital eleven to fourteen days later, during which time cervical changes favorable to induction had occurred. The castor oil and nasal drops were repeated and the membranes artificially ruptured. All four were delivered, three spontaneously, and one by midforceps following a fifteen-hour labor. The other woman entered spontaneous labor four days after dismissal from the hospital. In 30 patients (40 per cent), in addition to oil, drops and stripping of the membranes, the membranes were artificially ruptured to stimulate labor, either after it was established, or after it was found that cervical changes favorable to labor were present. In 12 (40 per cent), the membranes were ruptured at the time of stripping, and in 16 (60 per cent) rupture was reserved for a period of four or five hours after stripping was done. In 26 patients (34.7 per cent), oil was administered and the membranes artificially ruptured simultaneously. All of these, with the exception of one, entered labor with a latent period of less than six hours. The latter, with a latent period of nineteen hours, began labor following a series of 12 intranasal doses of pitocin and spontaneously delivered within seven hours.

It is therefore apparent that, by examination of the cervix in the office during the terminal thirty days of pregnancy, we have a means of satisfactorily predicting an approximate time for the onset of labor and, furthermore, are able to advise more accurately the nonresident patient of the measures she should take late in pregnancy in order to secure safe delivery, analgesia and amnesia during labor, a mature infant, and a minimum of maternal and fetal morbidity and mortality. If, after admission, one finds that changes have not occurred in the cervix as expected during the last two or three weeks, it is better to refrain from proceeding beyond the limit of stripping the membranes and permit the patient to proceed in pregnancy for another ten or fourteen days before reattempting to induce labor. The safety and wisdom of such a policy are illustrated by one of the cases. A multipara was examined in the office by the vaginal route thirty days and by rectal seven days before a date set for elective induction. At the elective time of admission the cervix had not undergone the expected changes, remained thick, firm, and closed. An attempt at induction was not made and she was dismissed from the hospital. Two weeks later and three weeks after the expected date of confinement, she spontaneously entered a sluggish labor complicated by primary uterine inertia which was terminated by midforceps twenty-five hours later. Failure to appreciate the fact that this case was not ready for labor two weeks earlier might have resulted in increased danger to the mother and her infant.

The fact that four other patients went eleven to fourteen days longer, after an attempt to induce labor by stripping the membranes, before developing changes in the cervix and lower uterine segment indicating that induction would be safe, is proof that one should proceed with caution in artificially rupturing the sac when induction is considered.

Briefly, therefore, vaginal examination under sterile precautions at intervals of four and two weeks of the expected date of confinement enables one to decide upon the approximate time of confinement or type of management of such cases. The ability to predict changes in the cervix indicative of term pregnancy is to be acquired by a careful interpretation and recording of changes which occur in the structure from week to week as pregnancy advances.

women. All of these lived at a distance of more than 50 miles from the hospital. All 35 received satisfactory analgesia and amnesia during labor. The average duration of labor was, in round numbers, nine hours—five hours shorter than the average for patients permitted to enter spontaneous labor at home. In 13 (37.1 per cent), spontaneous labor had its onset within eight days after the date selected for establishing residence nearer the hospital. Labor was induced with castor oil in 10 cases (toxemia 2, overdue 6), following establishment of temporary residence. The maternal and fetal morbidity and mortality were zero for this group.

Table IV is an analysis of 76 cases admitted to the hospital for induction of labor after cervical findings on pelvic examination in the office at some time during the previous thirty days had revealed evidence that labor would be of short duration or because the distance between the home and hospital was great, and in some cases, because the woman was unable to secure residence nearer the hospital.

Of these, 24 were primigravidas and 52 were multigravidas. In 69 (90.7 per cent), the vaginal examination made at the time of admission revealed cervical changes confirmatory of those expected seven days to four weeks earlier in selecting the date of admission as the proper one for inducing labor. In 7 (9.3 per cent), the preadmission examination had given a false impression of the findings; four by rectal, had been misinterpreted by the examiner on selecting a date for induction. One patient, examined by vaginal thirty days and rectal seven days before admission, was found to have a cervix unsatisfactory for induction at the time of vaginal examination when admitted. She was dismissed from the hospital, established residence near by, and entered a spontaneous twenty-five-hour labor, fourteen days later, three weeks after the original expected date of confinement. The labor was complicated by uterine inertia and terminated by midforceps delivery. Of the 76 cases thought ready for induction, 75 (98.6 per cent) were subjected to an attempt at induction. In 69 (92 per cent), it was successful, but in 6 (8 per cent), efforts short of artificial rupture of the membranes met with failure. One patient of five who failed to enter labor following routine preliminary medication and stripping of the membranes returned in spontaneous labor four days later with a distinct sour odor of the vaginal discharge, placenta, and membranes at the time of delivery. She was afebrile during labor and the puerperium. Of the 75 successful inductions, 74 (98 per cent) were delivered through the pelvis and one (2 per cent) by laparotrachelotomy because of uterine inertia complicating labor with a large fetus (9½ pounds). The maternal mortality was zero. Two infants (2.6 per cent), a 17-day prepartum diabetic at 8 months, and a 4 pound, 3 oz. premature associated with polyhydramnios, were lost. Three cases (4 per cent) of mild postpartum uterine infection occurred in this group.

TABLE V. METHODS OF INDUCTION OF LABOR, 75 CASES

| | NO. | PER CENT | SUCCESS | FAILURE |
|---|-----|----------|-----------|-----------|
| Castor oil | 3 | 4.0 | -- | -- |
| Castor oil and intranasal Pitocin drops | 5 | 6.6 | 4 (80%) | 1 (20%) |
| Oil, drops and stripping of membranes | 11 | 14.7 | 6 (54.5%) | 5 (45.5%) |
| Oil, drops, stripping and artificial rupture of membranes | 30 | 40.0 | 30 (100%) | -- |
| Oil and artificial rupture of membranes | 26 | 34.7 | 26 (100%) | -- |

Table V shows the methods and incidence of success and failure in the 75 cases in which an attempt was made at induction of labor. In 3 (4.0 per cent), castor oil alone was effective. In 5 (6.6 per cent) castor oil was supplemented by intranasal pitocin drops. One of these previously mentioned, in which it

THE NATURE OF DYSMENORRHEA*†

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ESTIMATES of the number of women who suffer from dysmenorrhea at some time in life vary. Combining all reports, one is justified in the statement that probably one-third of all young women in America are afflicted. The problem from a practical standpoint has been stated in a graphic fashion by Haman,¹ who calculated that approximately 140 million hours are lost annually due to this cause, and that this loss of time represents an entire year of work by approximately 58,000 women.

Throughout the past century many theories concerning the nature and etiology of dysmenorrhea have been advanced, each of which has been speculatively based upon discovery of new facts. Each has had widespread influence on the study and management of dysmenorrhea during the period of its popularity. An early theory revived by Sims² held that the condition arose from obstruction of the cervical canal. This idea was sustained for many years and gave rise to all sorts of manipulative procedures to maintain a straightened or patent cervical canal. These ranged from dilation and cervical pessaries to the operation of Dudley and Pozzi at the turn of the century. The frequent failure of those operations marked a decline in this idea.

Bell³ espoused the theory that the condition was caused most commonly by hypoplasia of the uterus. Since then, due to the discovery that in many cases there was no demonstrable pathologic entity to account for the condition, and since many cures were effected by placebos, the idea that dysmenorrhea is largely psychosomatic has been proposed. Haman⁴ found by use of a Perner sensimeter that these women were more sensitive to pain. The management based upon this concept has been directed to improving the general welfare of the individual by exercises, psychotherapy, and hypnosis. The psychic factor should never be forgotten because the whole symptom-complex is bound around the subjective sensation of pain.

With the advances made in endocrine research, especially those of Bourne and Burn,⁵ Novak and Reynolds,⁶ Robson,⁷ Newton,⁸ and others,^{9, 10} that estrogens were associated with contractions of the uterus, while progesterone was accompanied by reduction of the contractions, several theories arose that dysmenorrhea was endocrine in origin. These were given a considerable blow when Sturgis and Albright¹¹ found that large doses of estrogens administered early in the cycle abolished ovulation, and that the subsequent period was quite

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†Ciba Pharmaceutical Products, Eli Lilly & Company, and Frederick Stearns & Company have generously supported these investigations. The Pitressin and Pitocin were purchased on the open market. The acetylcholine chloride was supplied by Merck & Company.

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By the careful evaluation of such changes combined with a consideration of the parity, rapidity of previous labors, size of the fetus and pelvis, estimated date of confinement, and distance necessary to travel following onset of labor, one is not only able to secure uniformly satisfactory results, but insure the mother of adequate pain relief at the time of labor.

Conclusions

1. The management of pregnancy and labor in the nonresident patient constitutes a definite problem to the attendant.

2. Changes occurring in the cervix and lower uterine segment during the terminal weeks of pregnancy are consistent and, at present, offer the most valuable information as to the time of onset and type of labor to be expected.

3. The condition of the cervix, as determined by vaginal examination at four and two weeks of expected date of confinement, enables one to predict with a high degree of safety the time of confinement.

4. Rectal examinations fail to convey accurate information and are often the cause of false interpretations. Such examinations are of value only when checked by vaginal palpation prior to actual induction.

5. Vaginal examination, in the office, under sterile precautions, at the end of thirty-six and thirty-eight weeks of pregnancy does not increase the incidence of infection at the time of delivery.

6. When practical, nonresident patients should establish residence at a safe distance of travel to the hospital.

7. The administration of castor oil followed by series of pitocin drops intranasally offers a highly effective safe method of inducing labor. When not effective, the additional stripping of the membranes insures a higher degree of success without danger to the mother or fetus.

8. Artificial rupture of the sac should be reserved until labor has been initiated by conservative measures, or reserved for cases in which the cervix is well effaced, soft, partially dilated, and in close contact with the presenting part.

9. A uniformly successful plan of management in labor for nonresident obstetric patients, based upon statistical results, is desirable.

10. Such a plan of management developed in the care of 187 nonresident obstetric cases is herewith presented.

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or laterally; whether the pain is constant or intermittent, whether there is backache which radiates or not down the thighs or elsewhere. There may be epigastric distress, nausea with or without vomiting, lassitude, excessive nervous tension, and headache of variable onset, location, and duration. Many patients with dysmenorrhea bruise easily. It apparently is of more than chance occurrence that many of these patients are relatively free from constipation. The pattern in each patient seems to be quite constant, but may vary at alternating periods, possibly due to ovulation from one or the other ovary. The similarity of the pain to that of abortion or of labor is often graphically described by the patient and may be of definite significance. Apparently the cyclic phenomenon places additional stress upon the patient and exposes other subclinical conditions. If one is permitted liberal interpretation of the word dysmenorrhea, it could then be considered to cover any distress present during menses except, possibly, that of hypermenorrhea. Systems frequently involved include primarily the genital, but also the gastroenteric, nervous, cardiovascular, and urinary.

Every investigator must realize the tremendous psychologic influence of evaluating the entire subjective symptom of pain, and he must make all effort to as much objectivity as possible. Almost any type of therapy, even with apparently adequate controls, has been shown to be successful in the majority of patients in nearly any series studied. These treatments run the gamut of medical and surgical practices and, to name only a partial list, include psychotherapy, hypnosis, physical exercises, antispasmodics, sympathomimetics, analgesics, hypnotics, antihistamine drugs, placebos, anti-allergins, endocrines of all sorts—estrogen, progesterone, testosterone, pregnant mares serum, thyroid, surgical procedures, dilation of the cervix, stem pessaries, trachelorrhaphies, presacral sympathectomies. Since many of these treatments effect an “apparent” cure in the majority of cases, it is necessary to develop objective methods to evaluate the degree of the dysmenorrhea and its alleviation. The etiology of each portion of the symptom complex should be explored. Methods should be devised to duplicate dysmenorrhea symptoms in both normal and control patients, not only during menstruation, but also at other times. This leads to the study of the uterus itself and its adjacent and component parts including the nerve and muscle tissue and the vascular activities. This requires biochemical, physiological, and pharmacological techniques well known in the respective laboratories, and must be done by groups of clinicians and laboratory experts.

Many of the most productive leads in accumulating new facts in regard to the action of drugs, chemicals, and hormones have been obtained from animal work in laboratories of pharmacology and physiology. In some instances these observations have been applied directly to develop new theories in regard to the human uterus. This cannot be done safely until the work is repeated upon the human being, since the reactions may be markedly altered in the various species.

During the past twelve years at the University of Georgia School of Medicine extensive investigations of the human uterus have been conducted by the staff members of the Departments of Obstetrics and Gynecology, Pharmacol-

painless. While there is some disagreement with these later findings, in general they are being substantiated by most observers. However, without the influence of endocrine secretions no menstruation is possible, so they must certainly play a major part in the normal and abnormal sequences of menstruation. Probably their chief role consists in setting the stage preparatory to a multitude of reactions which occur in the myoneural, vascular, and endometrial tissues. Macht and Lubin¹² demonstrated the presence of a toxic substance in the menstruum, blood, saliva, and skin secretions of patients immediately before and during menstruation. This substance, which they believe is chemically related to oxycholesterin, they called menotoxin. Smith and Smith¹³ state that dysmenorrhea is caused by a menstrual toxin which they have isolated from the endometrium immediately preceding and during menstruation. They hope it may be possible to develop a specific antibody which may be useful in treating dysmenorrhea.

Within the past decade there has been a growing appreciation of the importance of myometrial activity as determined by intrauterine balloon studies in the human being. Moir,¹⁴ Wilson and Kurzrok,^{15, 16} and Bickers¹⁷⁻¹⁹ have revived the theory that in some way muscular contractions, with possibly other associated factors, are at the root of the painful condition. Much of the work, however, has been done with imperfect techniques and, furthermore, the presence of the balloon as a foreign body within the uterus has caused undeniable and unavoidable criticism.

The classification of types of dysmenorrhea has been an inevitable accompaniment of the progress in knowledge, and has probably served a useful purpose. The separation most commonly given in textbooks is the division into primary and secondary; the former being those instances in which the disorder has originated at or soon after the onset of menstruation, and is generally unaccompanied by demonstrable alterations of the pelvic anatomy. The secondary type is associated with some detectable pathology, the onset of which may or may not coincide with the onset of dysmenorrhea. However, there is no pathologic condition of the pelvis which has been shown to be universally associated with painful periods. It is common knowledge that extensive pelvic pathology infections, fibromyomas, marked displacement or flexion of the uterus, and apparent complete fixation by adhesions may be associated with no pain whatsoever at the menstrual periods. Very likely the pelvic pathology, whatever it may be, is only one of a large group of contributory factors. Even membranous dysmenorrhea is misnamed, because in some instances, in which the larger part of the endometrium is shed in one sheet, there may be no pain. Dysmenorrhea is generally assumed to be the main symptom of endometriosis. Yet Counseller,²⁰ in a large series of cases, has shown that the periods were associated with pain in only 47 per cent of instances. Consequently, it is here suggested that this classification has outlived its usefulness and now should be abandoned.

In studying the individual case one is struck by the multiplicity of subjective symptoms making up the dysmenorrhea complex. Probably in no two individuals are they exactly alike. There can be as many differences in the individual pattern as there are combinations of a score of minor alterations of the abnormal sensations experienced by the patient, such as the variable locations and character of the pelvic pain, whether in the region of the uterus itself

and intestines. The balloons which we insert serve as foreign bodies resembling the menstrual debris. The uterus responds to this load of the distended balloon by attempting to expel it, but gauze packed against the cervix prevents this. Pressure curves show that organized (Fig. 1 *A*, 1 *B*) and disorganized (Fig. 1 *C*, 1 *D*) contractions and a mixture of these types (Fig. 1 *B*) occur. The disorganized or mixed type like those illustrated in Fig. 1 *B* and 1 *C* were observed more frequently in the patients who have dysmenorrhea, while those like Fig. 1 *A* were observed more commonly in the control patients. Yet, no particular type of tracings is always associated with dysmenorrhea.

Uterine pressures at which patients complain of pain vary a great deal. When contractions are organized, uterine discomfort occurs near 40 to 100 mm. Hg, and uterine distress appears near 140 to 180 mm. Hg. Low back pain, however, may occur during organized contractions which develops only 30 mm. Hg pressure. If the uterus is placed under a heavy load by additional distention of the balloons, organized contractions have developed a peak pressure of 340 mm. Hg in one dysmenorrhea patient. The average pressure in dysmenorrhea patients under these conditions was 160 mm. Hg, though 250 mm. Hg has been observed in several patients. It is interesting that during parturition the uterus develops maximal pressures ranging only from 40 to 90 mm. Hg.²³

During menstruation the abdominal pain may be intermittent or steady. In those patients where it is intermittent in nature, low uterine pressures were present between contractions, see Fig. 1 *A*. Contractions in such patients have been described as coordinated or organized.²⁵ Patients who developed steady severe low abdominal cramps generally showed uterine contractions with high intercontraction tone, see Fig. 1 *B* and 1 *C*. Where the menstrual distress includes severe steady abdominal pain and frequently recurring intense cramps or "doubling up" pain, tracings similar to that illustrated in 1 *B* were obtained and the patient complains of the "doubling up" pain during the wavelike elevations of uterine pressure. However, a definite latent period is apparently present since the pain persists further down on the descending slope than the point which corresponds to its site of appearance on the upstroke. This suggests that other factors such as blood circulation are important in the pain. In the presence of high tone (see Fig. 1 *B* and 1 *C*), pain always is severe at much lower pressures, often with pressures of 40 to 80 mm. Hg as has been shown by Moir,¹⁴ Wilson and Kurzrok,^{15, 16} and Bickers.¹⁷⁻¹⁹ However, as shown by Fig. 1 *D*, an occasional patient does suffer severe pain even with pressures associated with contractions possessing low amplitude and low tone. This observation that pain can be associated with uterine pressures of only 10 to 15 mm. Hg definitely differs from all of the previous reports.

Two impressive and revolutionary observations were that the characteristic pain could be produced in all of the twenty-five patients by the injection of pitressin, or by stretching of the uterus by increasing the fluid in the balloon²⁵ (Fig. 2). Pitressin evoked the characteristic dysmenorrhea symptoms of any particular patient including such remote effect as headache.²⁵ It was found that an intrauterine balloon was not necessary, though with its presence a smaller amount of pitressin would evoke the symptoms, especially when the balloon

ogy, and Physiology. Pertinent studies upon various laboratory animals have been associated with similar investigations upon the human being. Using the Hamilton optical manometer^{21, 22} and very small single or multiple balloons inserted into the uterus, and with needles inserted into blood vessels, pressure changes even up to 400 mm. Hg may be recorded simultaneously, with as little as 0.01 c.c. of fluid alterations showing all changes to within $\frac{1}{200}$ second.²³⁻²⁵ This has permitted determination of exact intercontraction tone pressures which in some cases were as low as 2 mm. Hg. The system also permits exact measurements of the amount of distention of the uterine cavity.

The human uterus varies during the monthly cycle both in structure and irritability.²⁶ It has work to do, and its muscle tissue responds to stresses and loads in a manner similar to muscle tissue in other organs, such as the heart

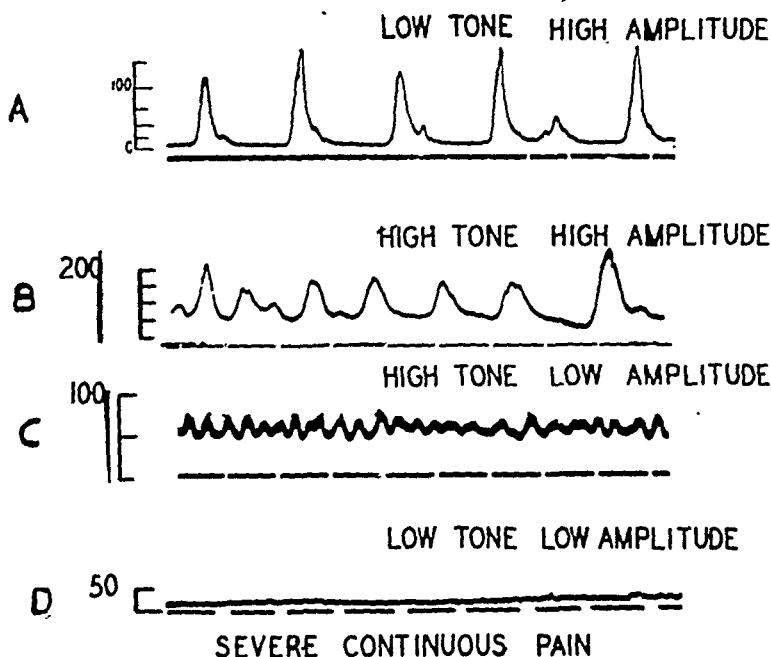


Fig. 1.—Human uterine pressure curves obtained during the first day of menses. The uterus is under a work load produced by distention of the intrauterine balloon. In all tracings time intervals of one minute are indicated on the base line, and the uterine pressures scale shows units of 50 mm. Hg unless indicated differently. The patients from whom the upper two tracings were obtained stated the abdominal distress was wavelike in nature; while those from whom the lower two tracings were obtained stated the abdominal pain was continuous and severe. Note the wavelike contractions on the upper two tracings and the nearly uniform pressure levels in the lower two tracings.

Fig. 1, A.—Patient, aged 25 years, para V, whose menstrual distress consists primarily of backache and legache with some low abdominal pains, intermittent in character and some headache. Her distress started after the delivery of her last pregnancy (twins) six years ago. During the illustrated pressure curves the abdominal pain appeared on the upstroke near 60 mm. Hg and lasted until the contraction curve was practically complete that is until the pressure had decreased to near 30 mm. Hg. The backache persisted and though it was markedly reduced in intensity, it did not completely disappear between contractions.

Fig. 1, B.—Patient, aged 27 years, para I, whose menstrual distress is severe, confines her to bed, and is relieved only by morphine. With every menses since menarche, the patient has experienced pain which quickly becomes intense. She complains of severe "doubling up" pains every two to four minutes superimposed upon a steady severe abdominal pain. She describes these pains as far more severe than those associated with childbirth. At the time this tracing was being recorded the menstrual distress was quite similar to that regularly present every month. The severe "doubling up" pains were experienced during each of the uterine pressure elevations and persisted on the downslope longer than the point corresponding to the time of their appearance on the upstroke.

Fig. 1, C.—Patient, aged 16 years, para 0, with severe steady abdominal distress. Note the absence of any large wavelike changes in uterine pressure, and that this patient experienced constant pain rather than intermittent pain.

Fig. 1, D.—Patient, aged 16 years, para 0. Note that severe continuous pain is present even though the uterine pressure is low. This is not typical, but has been observed in two patients who have painful menses.

was distended.²⁶ These symptoms did not occur after the injection of corresponding or even larger quantities of pitocin (Fig. 3). In fact, pitocin generally reduced the distress after the initial transient painful effect. Comparison of Fig. 3 with Fig. 2 shows that pitocin, histamine, and acetylcholine cause less increase in uterine activity than that caused by pitressin; also the contractions tend to remain better organized. At the present time in the search for new drugs which might relieve dysmenorrhea, various laboratories are spending considerable time, effort, and funds in evaluating chemicals and drugs as spasmolytic agents against acetylcholine and histamine. In certain cases²⁸ the use of the terms neurogenic and myogenic spasmolytic action have been applied to these drugs when they reduced the action respectively of acetylcholine and histamine on the uterus. Yet, in attempting to reproduce the exact type of painful reaction, it was found that the complete menstrual pain was never elicited by acetylcholine or histamine intravenously injected at the rate to produce distressing side reactions. This was true whether balloons were or were not inserted into the uterus. This may explain the poor results of the antihistaminic and anticholinergic antispasmodics when used upon the severer types of dysmenorrhea.

Nulliparous patients as a group accommodate less distention of the balloon than was tolerated by parous patients.²⁵ The average nulliparous dysmenorrhea patient tolerated 3 to 5 c.c., while control nulliparas tolerated on an average 4 to 7 c.c., and multiparous dysmenorrhea patients tolerated 5 to 9 c.c. Bearing a child apparently increases the tolerance of the uterus to stretch by enlarging the uterus. This may account for the relief of menstrual distress after bearing the first child in some, but certainly not in all individuals. One nulliparous patient could not tolerate as small an amount as 0.4 c.c. of fluid within the balloon (balloon occupied a minimal space of 0.8 c.c.). Such limited tolerance to the presence of 1.2 c.c. could well explain the menstrual distress in this patient and in those patients with an infantile type of uterus where edema and engorgement alone without the menstrual debris could well stretch the uterus sufficiently so as to cause menstrual distress. In such patients even when muscular activity was normal in type and was expelling uterine contents properly, the patient would experience continual distress intermittently intensified with uterine contractions.

Records were obtained simultaneously from three balloons inserted at different levels into the uterus and from one balloon inserted into the cervix. The position of the balloons is illustrated in Fig. 4 where they were overdistended with sodium iodide solution in order to visualize them by X-rays. Uterine pressure curves are different at various levels within the uterus both during organized contractions, see Fig. 5, and during disorganized contractions. There is a rather low correlation between fundal and cervical contractions. The latter are generally shorter and more frequent, whereas the musculature in the dome is slow to contract and even slower to relax. Downward from the dome of the fundus the uterine muscles progressively contract faster and relax more completely. The fact that different pressures exist in different portions of the uterus during menses allow organized contractions to propel menstrual debris

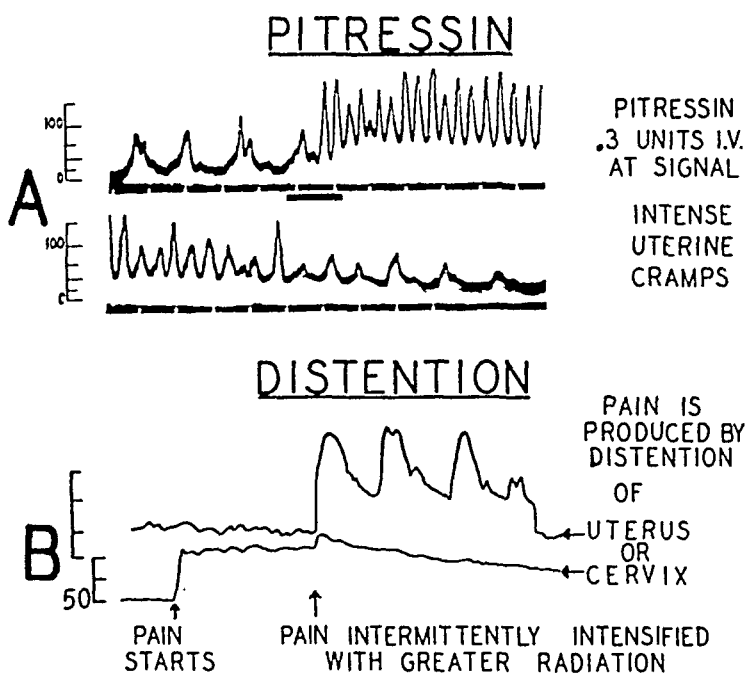


Fig. 2.—Injections of pitressin or distention of the uterus produced the characteristic symptoms of dysmenorrhea.

Fig. 2, A.—Uterine pressure curves from patient whose tracings are shown in Fig. 1, A, though these were recorded six hours later. Following the intravenous injections of 0.3 units of pitressin the patient complained of severe headache, backache, legaches, and intense uterine cramps and pain which became less severe after twenty to thirty minutes, but did not disappear until after receiving an analgesic after the elapse of one and one-half hours.

Fig. 2, B.—Uterine and cervical pressure tracings from a patient aged 27 years with dysmenorrhea since menarche. Menstrual distress includes severe headache, abdominal pain, and tenderness and, since the age of 18 years, "flooding" for one to nine days. Presacral nerve crush performed in 1941 afforded marked but incomplete relief of her menstrual pain. Estrogen and pregnandiol urine excretion and suction curettage indicate ovulation had occurred. Fluid added to or withdrawn from balloons at arrows. Note that pain was produced by adding 1/2 c.c. to the 1/2 c.c. already in the cervical balloon and intermittently intensified by adding 4 c.c. to the 1 c.c. already in the uterine balloon. Also note that the greater stretch upon the uterus was accompanied by a change from typical estrogenic to typical luteal contractions and that estrogenic type of contractions recurred when he stretch upon the uterus was reduced.

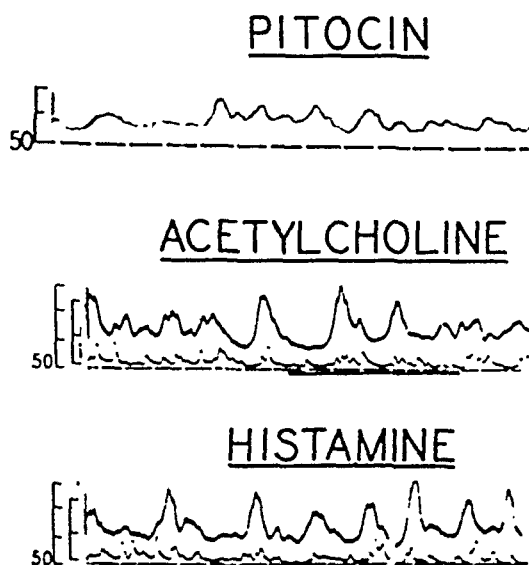


Fig. 3.—Tracings were obtained from same patient which supplied those in Fig. 1, A and Fig. 2, A; and were obtained five hours, three hours, and 2 hours before the injection of pitressin. Menstrual distress was not produced by the intravenous injection of 3 units of pitocin, 100 mg. of acetylcholine, nor 0.025 mg. of histamine, though patient stated she felt some activity low in the abdomen after the pitocin injection and some cutaneous warmth after each of the three drugs.

Main, and Patterson's²⁹ observations support this hypothesis. They reported dysmenorrhea like episodes in a patient who had congenital absence of the uterus which was replaced by muscular nodules at the proximal ends of the round ligaments. The painful periods occurred even after the surgical removal of the muscular nodes. Larkin³⁰ reported production of dysmenorrheal-like attacks in six women whose fundi had been removed. Other possible etiologic factors include: vascular congestion, inflammatory or cyclic edema, tissue or cellular fragility, vasoconstriction, and unusually low threshold for pain.

Studies now in progress show that during the premenstrual and menstrual periods the myometrium and blood vessels of some patients show a greater sensitivity to pitressin than was present during the late resting stage of the cycle. This heightened sensitivity also included the influence of pitressin upon water metabolism. A similar hypersensitivity to pitressin, acetylcholine, epinephrine, and histamine has been produced in rabbits, dogs, and cats by the administration of estrogens.³¹

These observations suggest the hypothesis that dysmenorrhea may result from a physiologic increase in sensitivity which varies in intensity and in type from patient to patient. This hypersensitivity may concern only the uterus or may involve other systems such as the gastroenteric, cardiovascular, and nervous systems, and thereby account for the particular dysmenorrhea symptom complex of a given patient. A tentative outline of the other factors contributing to dysmenorrhea is appended.

I. Mechanical obstruction which may be caused by: anatomic conditions such as juvenile type of uterus, cervical stenosis, malposition, fibroids, or scar tissue.

Infections where scar tissue, congestion, edema, and pus are factors.

Physiologic changes where excessive tissue fragility, membranous menstrual debris, cyclic edema and congestion of the uterus and tubes, and spasm producing contraction rings may be important contributory factors.

Obstruction also may occur in other systems since pylorospasm or cardiospasm are frequently observed immediately before and during menses in certain patients.

II. Insufficient circulation secondary to: cyclic edema and passive congestion, vasoconstriction, abnormal muscle activity, scar tissue, and anemia. The reproductive tract and the lumbar venous sinus generally are markedly effected but other areas such as the gastroenteric and urinary systems may also be influenced.

III. Disorganized muscular activity or excessive pressures developed by organized contractions of the uterus or tubes secondary to: menstrual debris, obstruction, an unusually small tolerance to distention of the uterus, nerve edema, high estrogen levels or unusual sensitivity to normal levels of estrogens.

IV. Very low threshold for sensory impulses: This may be the result of individual differences, excessive increase in irritability before and during menstruation, infection, presence of edema about nerves and nerve endings during the premenstrual and menstrual period, and/or presence of scar tissue. As a result uterine muscular response, pain perception, and vascular changes may be abnormally great.

V. Other contributory factors include: Excessive tissue fragility, emotional stress, menstrual toxins, vascular changes in the ovaries, and presence of other conditions such as allergy and intervertebral disc pathology.

downward and out of the cervical canal. Disorganized contractions or the development of a contraction ring, as was observed in one patient, may interfere with this milking action causing undue distention and pain in certain instances. Since different pressure curves are obtained from different parts of the uterus, single balloon tracings obtained from month to month may well differ from each other merely as a result of the location of the balloon, and may provide false ideas concerning drug action.



Fig. 4.—Roentgen visualization of four balloons inserted so as to record pressures simultaneously from the dome of the fundus, the main portion of the fundus, the lower uterine segment and the cervical canal. In this patient the balloons have been overdistended with 30 per cent solution of sodium iodide in order to obtain better visualization.

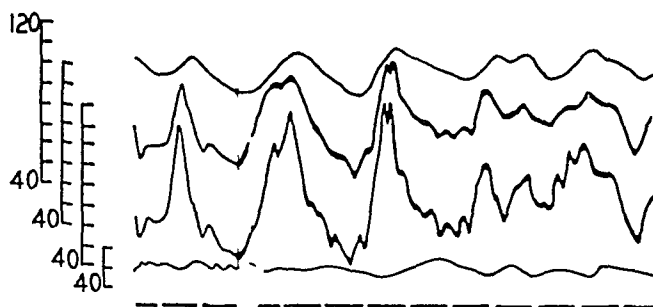


Fig. 5.—Multiple balloon tracings from the uterus of a patient aged 31 years with dysmenorrhea symptom-complex of steady low abdominal cramps with intermittent wavelike cramps. Note that pressure curves from different portions of the uterus differ from each other. Single balloon tracings obtained from month to month may well differ from each other merely as a result of the location of the balloon and thereby may lead to false ideas concerning drug action.

From the study to date it is justifiable to consider the menstruating uterus as functioning in a fashion similar to that in abortion or in labor with their respective puerperia, substantiating the idea that menstruation is an abortion of the decidual endometrium. Under load the myometrial action may become similar to that in abnormal types of labor.²⁷ The dysmenorrheic patients fall into loosely defined groups, some of whom are more or less true types such as the one described by Bickers with high pressure uterine contractions quite regular and accompanied by high intercontraction tones. These are the ones who respond well to spasmolytics such as magnesium ions which relieve the spasm. However, in many others there must be a multiplicity of factors besides the myometrial, all of which together produce the symptom complex. Spalding,

THE VALUE OF X-RAY STUDIES OF THE PELVIS IN OBSTETRICS*†

O. HUNTER JONES, M.D., CHARLOTTE, N. C.

IT HAS been observed that not infrequently obstetricians, in the management of their difficult cases, fail to avail themselves of the information to be gained from x-ray studies of the pelvis and fetal-pelvic relationship. This prompted the questionnaire, which was sent to every member of the South Atlantic Association, in an effort to find out just how often x-ray studies are used, what techniques are employed, and the value derived therefrom. Ninety-eight of the 122 questionnaires were answered. Five members limit their work to gynecology, thus leaving 93 questionnaires for analysis. Table I to IV show the results.

TABLE I.—INCIDENCE OF PELVIC X-RAY STUDIES

| OBSTETRICIANS | PER CENT OF CASES |
|---------------|-------------------|
| 3 | 0 |
| 16 (18%) | Not stated |
| 8 (9%) | 1 or less |
| 26 (29%) | 2 to 5 |
| 15 (17%) | 6 to 10 |
| 9 (10%) | 11 to 20 |
| 7 (8%) | 21 to 30 |
| 4 (4%) | 40 to 60 |
| 5 (5%) | 80 to 100 |
| — | |
| 90 | |

Incidence of Pelvic X-Ray Studies (Table I).—Three of the ninety-three obstetricians rarely, if ever, use x-ray studies. Sixteen fail to state the incidence, but it seems fair to assume that their incidence is between 1 to 10 per cent (1 to 5 per cent is probably more accurate), and for statistical purposes is so shown.

Eight of the reporting obstetricians use x-ray studies in 1 per cent or less of their cases; twenty-six in 2 to 5 per cent; fifteen in 6 to 10 per cent; nine in 11 to 20 per cent; seven in 21 to 30 per cent; four in 40 to 60 per cent; five in 80 to 100 per cent (including three who use x-ray in 100 per cent of their cases).

Combining the 1 to 5 per cent and 6 to 10 per cent groups, one finds that 49 (55 per cent) obstetricians employ x-ray studies in 1 to 10 per cent of their cases, and by including the sixteen obstetricians with unrecorded incidence the number becomes 65 (73 per cent). In other words, 73 per cent of the members of the South Atlantic Association, who answered the questionnaire, use pelvic x-ray studies in not more than 1 to 10 per cent of their cases. Furthermore, of the 73 per cent, twice as many use x-ray studies in 1 to 5 per cent of their cases as do those in the 6 to 10 per cent group!

*Read at the annual meeting of the South Atlantic Association of Obstetricians and Gynecologists, Savannah, Ga., Feb. 6 to 8, 1947.

†Based on questionnaire to the membership of the Association.

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x-ray as an important part of their obstetric armamentarium; one-third show a "lukewarm" interest in, and derive occasional benefit from these studies; the remaining one-third find little, if any, value in such studies (and have the lowest x-ray incidence!).

Discussion

It is not surprising to find that most of the obstetricians who rely on anteroposterior and lateral films alone, or who leave the choice of the film technique to the radiologist or technician, report little if any value derived therefrom. This is to be expected. Unfortunately, the technique and interpretation of pelvic radiography is not quite so simple. Many obstetricians have not been sufficiently interested to learn what a good technique consists of and what to expect from it. It must be remembered that the radiologist does not examine the patient. Therefore, his interpretation has to be correlated with the clinical findings, and for this reason best results are obtained when the obstetrician studies the films with the radiologist, or learns to read them himself. Allan Tuggle,³ radiologist of the Charlotte Memorial Hospital, has aptly expressed it when he said: "Accuracy of interpretation is dependent upon the skill and experience of the physician whether he be obstetrician or radiologist."

There are several methods of pelvic radiography which, in the hands of those who carefully carry out the originator's technique, are giving good results. In general, they range from the strictly quantitative, such as the Ball, to the qualitative, such as the Caldwell-Moloy, which stresses primarily the qualitative values, without much consideration of mathematically expressed diameters per se, through stereoscopic vision of the entire pelvis and fetal-pelvic relationship.

More recently the isometric method, which is really a combination of the quantitative and qualitative aspects of x-ray pelvimetry, has been described by Steele, Javert, and McLane.¹ McLane, however, has made an interesting statement: "I believe the qualitative method of Caldwell and Moloy is the best method we have for studying cephalopelvic disproportion, but you cannot sell it to the public. You must give measurements, you cannot sell an obstetrician relationships."

The replies received from the questionnaires seem to bear out McLane's statement. Only seven of ninety report using the qualitative method of Caldwell and Moloy. And yet there is considerable dissatisfaction on the part of many obstetricians with the other methods being used, as evidenced by the frequent complaint of the inadequacy of their x-ray studies. I am convinced that one reason why x-ray means so little to these obstetricians is that they think of it and use it only for measurements, and forget that information of greater importance than actual measurements is gained by studying the pelvis and fetal-pelvic relationship under stereoscopic vision, as originally stressed by Caldwell and Moloy. I thoroughly agree with D'Esopo⁴ when he says: "Personally, I feel somewhat lost when I try to evaluate the pelvis in terms of diameters. The stereoscopic view of the relationship between the head

By way of comparison, at the New York Lying-In Hospital,¹ pelvic x-ray studies are made on 7.6 per cent of the clinic cases and 20.3 per cent of the private patients.

At the Sloane Hospital for Women,² approximately 20 per cent of the clinic cases and 30 per cent of the private patients have x-ray studies.

In my private cases, the incidence approximates 25 per cent.

TABLE II.—TIME X-RAY STUDIES MADE

| | |
|-------------------------------------|----|
| Early in pregnancy | 3 |
| At or near term | 13 |
| At or near term and/or during labor | 74 |
| | — |
| | 90 |

Time X-Ray Studies Made (Table II).—Three obstetricians prefer x-ray studies early in pregnancy and occasionally repeated later; thirteen at or near term; seventy-four at or near term and/or during labor.

As would be expected, most studies are made at or near term, and less frequently during labor, when the relationship between full-term fetus and pelvis can be shown.

TABLE III.—X-RAY TECHNIQUE

| | |
|------------------------|----|
| Thoms-Torpin | 45 |
| Ball | 13 |
| Caldwell-Moley | 7 |
| Snow | 2 |
| Sussman | 1 |
| Walton | 2 |
| AP. and lateral | 5 |
| Combination of methods | 5 |
| Unknown | 10 |
| | — |
| | 90 |

X-Ray Technique (Table III).—Forty-five obstetricians use the Thoms-Torpin method (including modifications); thirteen use the Ball technique; seven use Caldwell-Moley; two use Snow; two use Walton; one uses Sussman; five use a combination of the various methods above; five use simply an antero-posterior and lateral film; ten do not know what technique is employed, being left entirely to the discretion of the radiologist or technician.

TABLE IV.—VALUE OF X-RAY STUDIES

| | |
|-----------------------------------|----|
| Invaluable, or extremely valuable | 15 |
| Helpful | 18 |
| Occasional x-ray helpful | 32 |
| Questionable value | 25 |
| | — |
| | 90 |

Value of X-Ray Studies (Table IV).—Fifteen obstetricians find pelvic x-ray studies to be invaluable, or extremely valuable; eighteen find them helpful; thirty-two find an occasional x-ray helpful; twenty-five find that x-ray studies are of very limited, or even questionable value.

In other words, approximately one-third of the ninety obstetricians find pelvic x-ray studies to be of real value, but only 50 per cent of this group use

to 1944, the cesarean rate on the ward service was 3.2 per cent, and on the private service 9.6 per cent. X-ray studies were used on both groups and used routinely for primiparas in the ward service. Thoms¹⁰ states that: "From our somewhat extended experience, we have for some time been convinced that, while a knowledge of the true capacity of the bony pelvis as revealed by x-ray may increase the incidence of cesarean section as an operation of choice over the difficult forceps or breech extraction, it is equally true that the employment of the operation will be decreased in such cases as unengaged head where disproportion is suspected but, when subjected to roentgen examination, does not actually exist."

At the New York Hospital,¹ where x-rays were taken routinely on certain groups of cases over a period of three years, there was a decrease in the number of cesareans done for disproportion, and also a decrease in the gross fetal mortality.

Stander states: "As a result of x-ray pelvimetry, the total incidence of cesarean section may not be markedly decreased, but this operative procedure should be performed more frequently upon correct indications, thus decreasing the unnecessary ones, at least these should be done more often at the proper time, instead of too late to be consistent with the best welfare of both mother and child."

At the Boston City Hospital,¹¹ the incidence of cesarean section for cephalopelvic disproportion in primiparas was reduced by 50 per cent, without jeopardizing the mother or baby, after adoption of x-ray pelvimetry.

At Sloane Hospital for Women,² for the past five years the ward cesarean incidence has ranged from 3.3 to 3.8 per cent, and the private patients twice this per cent. X-ray has not increased the incidence of cesarean section, but its use has permitted application to the proper cases.

Moley⁵ states: ". . . , in many instances, the information contributed by roentgenologic examinations has been a factor in saving fetal life. This is quite a far cry from criticisms offered in earlier years, that roentgenologic methods of examinations would result in a loss of skill in the use of our hands in obstetric maneuvers. I believe, on the contrary, an understanding of the varied mechanisms of labor and careful appreciation of the size of the pelvis and its shape has enabled us to perform correct maneuvers without the trial and error that frequently resulted in obstetric difficulty in the past."

Should pelvic x-ray studies be routine? Films on every primipara and on some multiparas is a desirable routine. However, it is not an actual necessity in the majority of cases, as a minimum of information can be obtained without it. The question of expense, as was so often referred to in the questionnaires, should not enter into the decision if x-ray study is thought to be indicated. The expense is not great, and surely the information frequently gained is worth "many fold" to the patient because of better obstetric results.

I would say that x-ray studies should be made in the following cases: (1) All patients with contracted pelves, questionable contraction, suspected disproportion, or with greatly abnormal architectural features, as revealed by vaginal examination; (2) all patients not previously x-rayed, whose labor is not progressing satisfactorily, unless one can be sure that no possibility of disproportion exists—if x-rayed previously, repeat x-rays during such a labor are at times indicated; (3) all patients with a history of difficult labor or

and the pelvis gives a three-dimensional concept which permits structural visualization that greatly augments the information that we obtain by digital examination."

In my practice, I use the Caldwell-Moloy technique with an ordinary stereoscope instead of the precision stereoscope. No attempt is made to take any pelvic measurements, except the anteroposterior diameter (true conjugate) when desired. This is measured by means of a centimeter lead ruler which is placed between the thighs on the lateral film. Thus the ruler has the same distortion as the film in this plane and gives an accurate measurement. The lateral film is taken with the patient lying down. However, it is claimed⁵ that the standing lateral has advantages over the supine lateral, particularly since it aids in allowing gravity to force the head to the lowest level.

My interpretation of the films then, for the most part, is a qualitative one, i.e., a study of the architecture of the complete pelvis, and of the relationship between the fetal head and the pelvis at term or during labor.

It has been shown that it is almost impossible to take accurate pelvic inlet measurements by vaginal examination. Several investigators, i.e., Steele, Wing, and McLane,¹ Thoms,⁶ and Dickinson and Procter⁷ have checked the true conjugate by x-ray against the diagonal conjugate method clinically and found very little correlation between the two. McLane concluded that clinical measurements on the pelvic inlet have no value. Of even greater importance, however, is the study of 1,000 cases, by x-ray pelvimetry, by Steele and Javert,⁸ who found that clinical measurement of the anteroposterior diameter of the inlet will reveal only one-half of the truly contracted pelvises.

Weinberg and Seadron,⁹ in a study of 350 cases x-rayed routinely ten days before term and the findings compared with the clinical examination, found that when both the clinical and x-ray prognosis agreed, the accuracy of prognosis was highest. When x-ray and clinical studies differed, x-ray prognosis was found to be three times as accurate as clinical prognosis.

Certainly x-ray gives a far more accurate impression of the shape and size of the pelvis, at all levels, than can be obtained from vaginal examinations alone. Frequently, x-ray simply confirms the findings from vaginal examination, in which case it is reassuring. However, there are many times when x-ray study reveals features in the pelvic architecture that one has missed entirely by vaginal examination. A good example is the size of the sacrosciatic notch or the shape and position of the sacrum. These factors may be of the greatest importance as regards the type of delivery anticipated, especially if it is to be operative.

Pelvic radiography should not, of course, take the place of careful vaginal examination. However, one should be aware of the limitations of, and at times erroneous impressions obtained from, vaginal examinations.

Answers to the questionnaires revealed the fear on the part of a number of obstetricians that the use of x-ray would lead to an increase in the cesarean section rate. However, this is not borne out by experience. For example, my cesarean rate averages 3.6 per cent. At the New Haven Hospital, from 1935

9. Pelvic radiography does not increase the cesarean section incidence. Its use aids in application of cesarean section to the proper cases.

10. Routine employment of pelvic radiography for certain groups of cases is advocated.

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delivery in previous pregnancies; (4) all primiparas, and some multiparas, with abnormal presentations, such as breech, transverse, brow, etc.; (5) elderly primiparas unless the pelvis is obviously ample; (6) fractured pelves, spinal and other deformities.

Questionnaires were answered by six of the seven medical schools located in the area of this association. Two schools report x-ray incidence of 5 per cent or less; one of 5 to 10 per cent; one of 60 per cent; one of 100; and one failed to give the incidence. This would indicate that not all of our schools are stressing the value of pelvic radiography to medical students and house staff. It is well to remember that it is primarily because some American medical schools have taken the lead, that many obstetricians throughout the country today have learned to derive a great deal of benefit from x-ray studies. As the interest in this valuable adjunct increases in all of our schools, so will the interest increase on the part of many members of this association.

Summary.

1. Questionnaires were sent to every member of the South Atlantic Association of Obstetricians and Gynecologists in an effort to learn the incidence of pelvic x-ray studies, techniques employed, and the value derived therefrom. Ninety-three questionnaires were analyzed.

2. The pelvic x-ray incidence varies from less than 1 per cent to 100 per cent. Sixty-five (73 per cent) of the members who answered the questionnaire, have an incidence of 1 to 10 per cent, but twice as many (of the 73 per cent) use x-ray studies in 1 to 5 per cent of their cases as do those in the 6 to 10 per cent group.

3. Most x-ray studies are made at or near term, and less frequently during labor.

4. Forty-five employ the Thoms-Torpin x-ray technique, thirteen the Ball technique, seven the Caldwell-Moloy technique, and the rest a variety of techniques. Many members are dissatisfied with the particular technique they are using.

5. The author uses the Caldwell-Moloy technique with an ordinary stereoscope. A centimeter lead ruler, routinely placed on the lateral film, gives the true conjugate measurement, when it is desired. Caldwell-Moloy technique gives information of greater importance than actual measurements.

6. Approximately one-third of the members find pelvic x-ray studies to be of real value, but only 50 per cent of this group use x-ray as an important part of their obstetric armamentarium; one-third show a "lukewarm" interest in, and derive occasional benefit from, these studies; the remaining one-third find little, if any, value in such studies (and have the lowest x-ray incidence!).

7. Questionnaires answered by six of the seven medical schools located in the area of this association indicate that not all of these schools are stressing the value of pelvic radiography to medical students and house staff.

8. X-ray studies may confirm clinical findings, or may reveal pelvic architectural features undetected by vaginal examination. One should be aware of the limitations of vaginal examination.

view. Also it should be remembered that organic illness may give rise to fears which exaggerate the symptoms of the patient.

The incidence of psychosomatic problems encountered by the authors has been of interest, since our practice consists of a group of patients who are referred directly for consultation. Those patients not referred in the usual sense were the wives of physicians and others associated with the institution. Emotional problems were felt to be frequently responsible for many of the symptoms leading to consultation for the first group. For this reason, an analysis of the incidence of psychosomatic disease seemed worth while. The purpose of this paper is to call attention to this problem and to evaluate the frequency of its occurrence. Many of our patients had failed to respond elsewhere to adequate treatment of a pathologic lesion because an associated unsolved psychologic problem was present. Other patients were referred for various operative procedures which were unnecessary after solution of a fundamental emotional problem. It is interesting to note that some of them had one or more operations for the existing symptoms without relief.

Material

The patients studied consisted of the private office patients of two specialists in obstetrics and gynecology over a period of five years. For this reason, many acute and common obstetric and gynecologic complications do not appear, since the patients were sent directly into the hospital without first being seen in the office. The total number of patients subjected to analysis was 1,759. These patients ranged in age from 8 months to 82 years. All of the patients were referred and of the white race. Three major groups were recognized.

1. Group 1 were patients who presented sufficient diagnostic pathologic findings to account for their symptoms.
2. Group 2 had symptoms in excess of the physical findings.
3. Group 3 were patients characterized by numerous symptoms which could not be explained by any physical signs.

The following distribution of patients was found:

TABLE I. GENERAL DISTRIBUTION

| GROUP | GYNECOLOGY | OBSTETRICS | TOTAL | PER CENT |
|-------|--------------|-------------|-------|----------|
| 1 | 853 | 338 | 1191 | 67.6 |
| 2 | 180 | 40 | 220 | 12.6 |
| 3 | 331 | 17 | 348 | 19.8 |
| | 1364 (76.6%) | 395 (23.4%) | 1759 | 100.0% |

A total of 32.4 per cent fell into Groups 2 and 3 which was an index of the incidence of psychosomatic disease. For convenience the patients were further subdivided into certain categories, some of which will be defined and illustrated by a short case report.

Group 1 consists of those patients who had organic pathology to account fully for their symptoms. A total of 1,191 patients had clear-cut pathologic problems. Tables II and III list the diagnoses encountered in this group.

THE INCIDENCE OF PSYCHOSOMATIC DISEASE FROM A PRIVATE REFERRED GYNECOLOGIC PRACTICE*

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THE fundamental mechanism of functional disease has been appreciated only by the psychiatrists until recently. During the last decade emphasis has been placed on psychosomatic disorders. The practitioner now appreciates that symptoms of organic disease frequently appear as a result of emotional and psychologic disturbances. Such functional disorders actually create disability equal to that resulting from organic pathology. In some cases there are actual physical changes simulating organic lesions, i.e., the spastic colon; pseudocyesis and others.

The attitude of the public in regard to psychosomatic disorders, has changed under the stimulus of the wide publicity given to the war neuroses. Prior to this, psychoneurosis was considered an insulting term to the patient to whom it was applied. Often the implication of malingering was suggested by the diagnosis. Furthermore, until recently many medical schools have taught only the organized psychoses and have neglected the less dramatic functional disorders. Each department of these schools relegates the discussion of such disorders to psychiatric classes which are assigned only a small portion of the curriculum. In contrast, one school teaches that 80 per cent of the patients in the gastrointestinal clinic have functional complaints.

The diagnosis of psychosomatic disease rests upon two points:

1. The absence of any demonstrable organic pathology or a lesion sufficient to cause the patient's complaints.
2. The presence of a definite emotional problem grave enough to justify such a diagnosis.

The absence of a demonstrable pathologic lesion does not necessarily rule out a serious or fatal organic lesion which may not be detected by our present diagnostic methods. Occasionally all physicians are embarrassed when a patient under treatment for a presumed functional disease develops signs of a serious ailment. Each of the above criteria *must* be present for a diagnosis of psychosomatic disease.

Some physicians seek to explain all illnesses on an organic basis without considering that emotional factors may create misleading and bizarre symptom complexes; others overemphasize the psychologic background. The practitioner must keep in mind that both functional and organic problems occur in every practice, and must analyze each patient carefully from these points of

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even fear of death. Many of the patients improved strikingly shortly after the exact character of their illness is explained to them. Typical examples are illustrated by the following case records:

Group II A.—Mrs. J. G. W., NCBH No. 25837, aged 20 years. Patient complained of amenorrhea of nine months' duration. She also complained of general malaise, lassitude, headaches, and lower abdominal discomfort. Prior to the period of amenorrhea, she had a regular menstrual interval of twenty-nine to thirty days, with bleeding of four to five days' duration. She had reached menarche at 13 years of age, and her secondary sexual characteristics appeared in the usual order.

General physical examination revealed no gross abnormalities except the presence of a cyst of the right ovary approximately 4 cm. in diameter.

A tentative diagnosis of a corpus luteum cyst was made, and the patient was reassured. She reported three weeks after her initial examination that her symptoms had rapidly improved and that she felt entirely well. One month later she had a normal menstrual period, followed by two months of amenorrhea, with the recurrence of her original symptoms. Her symptoms again disappeared after reassurance.

She then resumed a normal menstrual cycle, which continued during three years of observation. The ovary returned to normal size and consistency under observation.

Group II B.—Mrs. A. L. C., NCBH No. 28716, aged 36 years. This patient had three major operations, an appendectomy, a nephrotomy for a pyonephrotic kidney, and a laparotomy for adhesions. She also had a dilatation and curettage and cauterization of the cervix and four additional hospital admissions. She had been treated by numerous physicians in her home community and had been to two medical diagnostic centers. Her complaints were myriad, but the principal ones were related to her abdomen and genitourinary system.

The gynecologic examination revealed no gross abnormality of the pelvis. The vaginal mucosa was slightly reddened, and fresh, wet preparations revealed the presence of *Trichomonas vaginalis* organisms.

The patient complained bitterly of profuse leucorrhea. She was seen on seven occasions during a two-year interval, and although each examination was made a full week after the patient's last douche, only a slight amount of secretion, slightly exceeding normal, was found in the vaginal vault. No other evidence of unusual leucorrhea was found.

Group III contained 348 patients who had symptoms in the absence of explanatory demonstrable pathology and, in addition, had emotional conflicts of sufficient severity to explain the complaints. They have been divided into nine somewhat arbitrary subgroups, using "The Standard Nomenclature of Disease" for diagnostic terminology. It is obvious that final diagnosis in these patients requires repeated interview and examination. Consultation with a psychiatrist was frequently refused because of the patient's conviction that pelvic pathology is present. These patients usually are beginning or have been on an endless round of medical consultations. The average course is a needless operation, treatment by a charlatan, or, occasionally, well directed psychiatric assistance. Many of the patients in this group have been endlessly treated for endocrine deficiency without avail. General diagnoses were made and are tabulated in Table V.

The following brief case reports illustrate some of the typical records in these subdivisions.

TABLE II. GYNECOLOGIC DISEASE

| | |
|--|-----|
| 1. Endometrial dysfunction | 183 |
| 2. Benign cervical lesions | 124 |
| 3. Pelvic relaxation, displacement, and Fistulae | 109 |
| 4. Primary dysmenorrhea | 101 |
| 5. Vaginitis | 100 |
| 6. Sterility | 89 |
| 7. Fibromyomata uteri | 70 |
| 8. Gynecologic check-up | 68 |
| 9. Pelvic inflammatory disease | 65 |
| 10. Pelvic malignancy | 36 |
| 11. Menopausal syndrome | 28 |
| 12. Benign ovarian lesions | 23 |
| 13. Vulvitis | 16 |
| 14. Bartholinitis and cyst | 9 |
| 15. Midmenstrual pain | 8 |
| 16. Premenstrual tension | 7 |
| 17. Congenital anomalies | 6 |
| 18. No disease or undiagnosed | 90 |

TABLE III. OBSTETRIC DISEASE

| | |
|---------------------------|-----|
| 1. Intrauterine pregnancy | 161 |
| 2. Incomplete abortion | 11 |
| 3. Ectopic pregnancy | 6 |
| 4. Missed abortion | 4 |
| 5. Habitual abortion | 4 |
| 6. Septic abortion | 3 |
| 7. Hydatidiform mole | 2 |

Included in this group are 215 patients who had apparent gynecologic symptoms due to disease in other systems or gynecologic disease secondary to pathology in other organs. For this reason, a complete history and physical examination is a part of each consultation. For example, backaches are often the presenting complaint to the urologist, orthopedist, and gynecologist.

TABLE IV. OTHER DISEASES

| | |
|--------------------------------------|----|
| 1. Urologic disease | 38 |
| 2. Orthopedic disease | 20 |
| 3. Diseases of ear, nose, and throat | 3 |
| 4. Neurologic diseases | 6 |
| 5. Adhesions and painful scars | 12 |
| 6. Dermatologic diseases | 4 |
| 7. Exogenous obesity | 34 |
| 8. Cardiovascular diseases | 22 |
| 9. Benign gastrointestinal disease | 18 |
| 10. Malignancy (extra-pelvic) | 5 |
| 11. Endocrine | 28 |
| 12. Hematologic | 3 |
| 13. Diseases of the venous system | 6 |
| 14. Pulmonary disease | 5 |
| 15. Benign tumors | 5 |
| 16. Infectious disease | 5 |
| 17. Deficiency status | 1 |

Group II included 220 patients whose complaints could not be clearly justified by the existing pathology. They are subdivided into Group A with mild and Group B with severe disproportion between the pathology and symptomatology. This difference is commonly due to emotional conflicts related to the pelvic disease, such as fear of loss of sexual function, cancer operation, or

Examination revealed a fixed retroflexion with thickening in both adnexal regions. Air studies and a salpingogram revealed occlusion of the tubes. She subsequently returned with the complaint of indigestion, nausea, vomiting, dizziness, and numerous other aches and pains. The internist who saw the patient did not know of her previous visit and felt that her difficulty was of a functional nature and treated her accordingly.

The second patient was 31 years of age, who was first seen because of vaginal discharge and arthritis. This discharge occurred prior to her marriage. She admitted to premarital intercourse of many years' duration. She was subsequently treated for arthritis of gonococcal origin, the organism being cultured after several tries from the vaginal discharge. Following her first hospital stay she had a criminal abortion, her husband being overseas. Her arthritis gradually improved with occasional flare-up. She has now left for a more favorable climate, and on last record was said to have been well.

The youngest sister was 21 years of age and single. Her chief complaint consisted of amenorrhea, leucorrhea, and loss of weight. She, too, gave the history of frequent intercourse since her menarche and stated that the man with whom she had been having intercourse recently was planning to marry her soon. Pelvic findings were questionable so that a Friedman test was carried out, which was found to be positive. She then stated that she was going to get married immediately and was not seen for two months. When she returned, it was for a check-up following a criminal abortion.

Group D. Dyspareunia.—Mrs. L. M. L., NCBH No. 31480. This patient was 34 years old and was married three years and divorced, and she had been remarried for one and one-half years at the time she was seen. She stated that her sexual relationships in both marriages were extremely painful and unsatisfactory. She described the pain as being on intromission as well as throughout the whole sexual act, and following intercourse continuous low abdominal pain with nausea and vomiting. Examination showed a perfectly normal pelvis with marked spasm of the pelvic floor muscles. This spasm could be relaxed by persuasion, which was frequently necessary during the examination. She returned later with the complaints of dysmenorrhea, et cetera, announcing that she could no longer stand the pain associated with intercourse and had separated from her second husband for that reason.

Group E. Phobias.—Mrs. B. E. H., NCBH No. 55233, aged 34 years. Her chief complaint was that life was not worth living and in addition had some complaints referable to practically every major system of the body. Further questioning revealed frigidity as an outstanding complaint.

The patient had been married for eighteen years. Her sexual responses were normal early in her marriage, with full orgasm occurring after the first three months of marriage. She was married when she was 15 years of age, and stated that her husband took advantage of her and that her choice of marriage partner was not a wise one. Her first child was born when she 15 years old and weighed 12 pounds. She had a very hard labor, two subsequent normal pregnancies, and several abortions.

Her husband is 43 years of age, inattentive, and does not understand her at all. They were staying together only because of the children. They practiced coitus interruptus for contraception, and she was in constant terror of conceiving again. Her indulgence in coitus was purely from the point of view that it was a marital duty.

She was intelligent and realized that her frigidity began after she had developed the phobia about the pregnancy, and all of her other complaints appeared subsequent to this problem. All of the usual diagnostic methods revealed no pathology.

TABLE V. PSYCHIATRIC DISEASES

| | |
|-------------------------------|-----|
| A. Psychosis | 16 |
| B. Psychoneurosis | 130 |
| C. Simple adult maladjustment | 82 |
| D. Dyspareunia | 12 |
| E. Phobias | 59 |
| F. Frigidity | 32 |
| G. Pruritis vulvae | 10 |
| H. Hyperemesis gravidarum | 5 |
| I. Miscellaneous | 7 |

Group A. Psychosis.—Mrs. S. C. K., NCBH No. 7135. This patient was a 27-year-old para i, gravida ii, who had for the previous seven years suffered from what she described as "fainting spells." The consulting psychiatrist, however, stated that these were catatonic episodes. She was referred because of early pregnancy complicated by schizophrenia. Physical examination revealed early intrauterine pregnancy. There were numerous scars over the skin as a result of burns and injuries during her catatonic attacks. She was almost totally uncommunicative, her history being obtained entirely from her husband. Therapeutic hysterotomy and a tubal ligation were done through a Pfannenstiel incision. On her fifth postoperative day she suddenly appealed to the house staff not to be allowed to go home from the hospital. Her reason for this was that if she went home again, her father-in-law would insist upon sexual relations while her husband was still out in the fields. She further stated that her mother-in-law knew this, but both of them were afraid to say anything to the husband about it. When this request was not granted on the following day, she removed her dressing and pulled open the incision, which was resutured. Her story was investigated and found to be probably correct. At this point, however, the father-in-law stepped in and forced the husband to sign a release. She subsequently recovered in another hospital but is now in the same mental state.

Group B. Psychoneurosis.—Mrs. P. T. Y., NCBH No. 38652, aged 24 years. This patient was a buxom farm girl who took great pleasure in elucidating her many problems. She took a bath, a douche, and an enema each day. She had dyspareunia, which was becoming progressively worse every day. She was firmly convinced that coitus is a woman's worst experience, and frankly advised her husband of this fact after each sexual experience.

She had one child 5 years of age, and her prenatal course was complicated by vomiting to the last day. Her labor and delivery were normal, but her lurid description of this process was astounding.

Her menstrual history was equally remarkable with vaginal bleeding occurring whenever she was nervous, a pint of black blood gushing from the vagina on occasions, large pieces of red flesh passing at times, and she was bed-ridden with pain a minimum of forty-eight hours each month.

The patient had equally dramatic symptoms referable to every major system, but no organic pathology could be demonstrated by any available method.

Group C. Simple Adult Maladjustment.—Mrs. A. D. H., NCBH No. 54512, Mrs. W. W. B., NCBH No. 30290, and Miss V. A. D., NCBH No. 38925. These three patients were sisters presenting the same basic problem. The eldest was 34 years of age when first seen, with the chief complaint of sterility. On investigating her history further she confessed that at the age of 16 years she had had intercourse with a number of different men and had apparently developed an acute gonorrheal infection. She continued this sexual promiscuity until she was married at the age of 23 years, but states that she is now loyal to her husband.

TABLE VIII. PREVIOUS OPERATIONS

| | GROUP 1 | GROUP 2 | GROUP 3 | TOTAL | PER CENT |
|------------|---------|---------|---------|-------|----------|
| 0 | 1093 | 173 | 279 | 1545 | 88.0 |
| 1 | 80 | 27 | 44 | 151 | 8.4 |
| 2 | 11 | 19 | 19 | 49 | 2.8 |
| 3 and over | 7 | 1 | 6 | 14 | 0.8 |
| | 1191 | 220 | 348 | 1759 | 100.0% |

The final analysis dealt with the ultimate disposition of the patient which may be seen from Table IX. The figures in Table IX reveal that in general management of a patient was largely medical, since 76 per cent were handled accordingly. Dilatation and curettage and treatment of cervical lesions are included in the surgical procedures. The only psychiatric referrals were in group 3. In spite of the large number of patients in this group (348), only 25 would accept psychiatric care. We feel that this is due to the number of pelvic complaints based upon psychogenic factors.

TABLE IX. DISPOSITION

| | GROUP 1 | GROUP 2 | GROUP 3 | TOTAL | PER CENT |
|-------------|---------|---------|---------|-------|----------|
| Medical | 891 | 182 | 294 | 1367 | 76.0 |
| Surgical | 300 | 38 | 29 | 367 | 21.7 |
| Psychiatric | 0 | 0 | 25 | 25 | 2.3 |
| | 1191 | 220 | 348 | 1759 | 100.0% |

Discussion

Whereas from the preceding figures psychosomatic disease is certainly not predominant, it is still a common phenomenon in gynecologic practice. A total of 568 patients, one-third of all of the patients exhibited some emotional disturbance. This figure is not as high as in some other specialties, but is still sufficient to demand attention. These phenomena occur more frequently in association with certain physiologic functions of the female, which are marital function and childbearing. Ignorance and fear seem to be the most important contributing factors. In general, the analysis revealed that there is little specific information in regard to the etiology of psychogenic disease in the preceding statistics.

Conclusion

1. The incidence of psychosomatic disease in a referred gynecologic practice is approximately 33 per cent.

Group F. Frigidity.—Mrs. B. F. F., NCBH No. 31437, aged 32 years. Patient complained that since the delivery of her baby she has had a progressive loss of libido, which has been closely correlated with diminishing sexual responses until sexual anesthesia is now present.

Shortly before the patient became pregnant, she learned that her husband had had a diagnosis of a congenital syphilitic infection made during his childhood. Shortly after their marriage it was determined on good authority that such an infection had never existed. The patient felt that her husband had been dishonest since he had not told her of this questionable syphilitic infection prior to their marriage. The emotional conflict resulting from this problem reached a point of crisis with the delivery of her baby, since during the entire pregnancy she has brooded over the possibility that her child might be deformed or might have some manifestation of this disease. Each day she looked for some evidence of syphilis in the child after its delivery and found herself constantly watching for some sign of a venereal disease in her husband. She was an intelligent woman and realized that this was directly related to her frigidity and had actually resulted in sexual aversion. No demonstrable pathology was present to account for numerous symptoms referable to every major system.

The patients were analyzed statistically from four viewpoints, the first of which was distribution according to age. This may be seen in Table VI. No significant factors were noted except the expected preponderance of patients in the active sexual life, i.e., 20 to 50 years (84 per cent).

TABLE VI. AGE DISTRIBUTION

| | GROUP 1 | GROUP 2 | GROUP 3 | TOTAL | PER CENT |
|-------------|---------|---------|---------|-------|----------|
| 0-20 | 100 | 18 | 30 | 148 | 8.5 |
| 21-30 | 521 | 101 | 132 | 754 | 43.0 |
| 31-40 | 330 | 62 | 116 | 508 | 28.0 |
| 41-50 | 153 | 33 | 49 | 235 | 13.0 |
| 50 and over | 82 | 28 | 4 | 114 | 7.5 |
| | 1191 | 220 | 348 | 1759 | 100.0% |

Secondly, an effort was made to determine any effect of occupation on the distribution of the patients. The occupational distribution of the patients is illustrated by Table VII. Again there is no conclusive evidence that occupation has any relationship to psychosomatic disease.

TABLE VII. OCCUPATION

| | GROUP 1 | GROUP 2 | GROUP 3 | TOTAL | PER CENT |
|---------------|---------|---------|---------|-------|----------|
| Housewife | 829 | 141 | 234 | 1204 | 69.5 |
| Business | 119 | 27 | 41 | 187 | 10.4 |
| Professional | 111 | 23 | 18 | 152 | 8.5 |
| Industrial | 65 | 19 | 21 | 105 | 5.7 |
| No occupation | 36 | 4 | 19 | 59 | 3.2 |
| Student | 31 | 6 | 15 | 52 | 2.7 |
| | 1191 | 220 | 348 | 1759 | 100.0% |

The third analysis involved previous operations to which the patient had been subjected, and Table VIII is a breakdown of these figures. There is in the preceding table a definite tendency toward an increased number of previous operations in groups 2 and 3.

TABLE I. CESAREAN SECTIONS—1935 TO 1946 INCLUSIVE

| YEAR | CASES | DELIVERIES | OUR CASES | REFERRED CASES |
|------|-------|------------|-----------|----------------|
| 1935 | 10 | 152 | 7 | 3 |
| 1936 | 13 | 165 | 10 | 3 |
| 1937 | 13 | 149 | 10 | 3 |
| 1938 | 16 | 142 | 11 | 5 |
| 1939 | 25 | 181 | 15 | 10 |
| 1940 | 24 | 250 | 13 | 11 |
| 1941 | 40 | 314 | 23 | 17 |
| 1942 | 38 | 455 | 30 | 8 |
| 1943 | 52 | 543 | 30 | 22 |
| 1944 | 56 | 520 | 41 | 15 |
| 1945 | 65 | 482 | 48 | 17 |
| 1946 | 65 | 582 | 37 | 27 |
| | 416 | 3935 | 275 | 141 |

TABLE II. CESAREAN SECTIONS IN 3,935 DELIVERIES

| | |
|------------------------------------|--------------------|
| Total | 416 in 3,935—10.5% |
| (Referred | 141 in 3,935— 3.6) |
| (Personal | 275 in 3,935— 6.9) |
| 34.3 per cent of sections referred | |

Disproportion (211 cases) provides the largest number both in the personal group (138) and the referred (73) group. We recognize that a wide difference of opinion exists as to what constitutes disproportion. We believe that x-ray study of all of these cases has no doubt increased the number of sections, but in so doing has increased the proper application of cesarean section. We believe that *many* could have been delivered vaginally with or without x-ray study. X-ray has been of untold value in giving information which would cast suspicion as to the outcome of the labor. We employ x-ray diagnosis as an aid in determining the various degrees of disproportion, including contracted midpelvis and outlet, and designating in some cases the position of the presenting part. We use the x-ray extensively in estimating maturity of the fetus, the location of the placenta, number of babies, and detection of malformation of fetal skeleton. We believe that this plan has eliminated severe complications associated with prolonged labor, uterine inertia, and hemorrhage, which have contributed so largely to both mortality and morbidity of the mother and death of the child.

During the past three years (thirty-six months) we have averaged 18.2 x-ray pelvimetries per month, or 657 x-ray pelvimetries in 1,584 deliveries, which is 41.5 per cent of all deliveries in the past three years.

We have used for the past six years the figures outlined by Snow in his book as a working basis in helping us decide the termination of the pregnancy.

Placenta Previa and Premature Separation of Placenta.—A total of 61 cases come under this heading. We do not follow the plan of doing sections on all placenta previas, nor do we section all abruptio placentas. X-ray has given us great help as an adjunct in diagnosis of placenta previa. We section all central placenta previas. X-ray has often picked up cases of placenta previa before bleeding began, and has accounted for some soft parts dystocia. Some cases of marginal and lateral placenta previa were sectioned because of the amount of bleeding and the condition of the cervix. We use a similar plan for premature separation of the placenta. To increase the gestation and viability of the baby, we have kept selected cases of placenta previa in bed in the hos-

AN ANALYSIS OF 416 CONSECUTIVE CESAREAN SECTIONS*

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AN ANALYSIS OF 416 CONSECUTIVE CESAREAN SECTIONS

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THE purpose of this presentation is to analyze critically a consecutive series of 416 cesarean sections which we have done during a twelve-year period from Jan. 1, 1935, through Dec. 31, 1946. We primarily are trying to evaluate our results; inasfar as they apply to us, to determine the results regarding mortality, morbidity, and fetal deaths. Maternal mortality, preventable stillbirths, and neonatal death statistics have steadily improved during the past twelve years, but as long as some deaths are preventable this condition cannot be regarded as satisfactory. We are aware that cesarean section is regarded by many as a large contributor to maternal mortality, and this is probably correct under certain conditions; however, we believe that the study of these cases may throw some light on this subject to the contrary.

In this study we have divided the 416 cesareans under consideration into two groups. The first group of 275 cases are patients who came directly to us as private patients, not referred by any physician, or were referred early in pregnancy. Many obviously came to us because they had undergone previous obstetric difficulty; others anticipated trouble and sought special care; and still others had been under our care during previous pregnancies. The important fact is that we were able to give what we consider good prenatal study before the advent of labor.

The second group consists of 141 patients referred to us by another physician or clinic, either late in pregnancy, in labor, or the emergency of the case had already existed. Many of the patients were referred during the pregnancy because major obstetric difficulty had been anticipated. Many received little or no prenatal care, and some received good prenatal care by the attending referring physician. The important fact is that we were not able to study the majority of this group before the advent of labor.

Table I shows the distribution of cases, the number of deliveries, personal cases, and referred cases from 1935 to 1946 inclusive.

Table II indicates that in 3,935 deliveries there were 416 sections, or 10.5 per cent. There were 275 personal cases in 3,935 deliveries, or 6.9 per cent; 141 referred cases in 3,935 deliveries, or 3.6 per cent. Of the 416 sections, 141 were referred cases, or 34.3 per cent.

*Read at the annual meeting of the South Atlantic Association of Obstetricians and Gynecologists, Savannah, Ga., Feb. 6 to 8, 1947.

TABLE IV. VARIATIONS IN PELVIC MEASUREMENTS

| | | SMALL | MEDIUM | LARGE |
|---|-------|------------|--------------|------------|
| Inlet | A.P. | Below 10.5 | 10.5 to 11.5 | Above 11.5 |
| | Tr. | Below 11.5 | 11.5 to 12.5 | Above 12.5 |
| Mid-pelvis | Total | Below 22.0 | 22.0 to 24.0 | Above 24.0 |
| | A.P. | Below 11.0 | 11.0 to 12.0 | Above 12.0 |
| | B.I. | Below 10.0 | 10.0 to 11.0 | Above 11.0 |
| | Total | Below 21.0 | 21.0 to 23.0 | Above 23.0 |
| Outlet | P.S. | Below 6.5 | 6.5 to 8.0 | Above 8.0 |
| | B.T. | Below 9.5 | 9.5 to 10.5 | Above 10.5 |
| | Total | Below 16.0 | 16.0 to 18.5 | Above 18.5 |
| Clinical Roentgenology of Pregnancy—Snow, 1942, p. 46 | | | | |

TABLE V. TYPES OF SECTIONS

| | OUR CASES | REFERRED CASES | PER CENT |
|-------------------|-----------|----------------|----------|
| Munro-Kerr | 240 | 115 } | 93.7 |
| Beck | 23 | 12 } | |
| Porro | 5 | 5 } | 2.3 |
| Low classical | 4 | 1 } | 2.1 |
| Classical | 1 | 3 } | |
| Water's | 1 | 2 | .7 |
| Smith's exclusion | 1 | | .2 |
| Post mortem | | 2 | .5 |
| Ovarian term | | 1 | .2 |
| Total | 275 | 141 | 100 % |

TABLE VI. OTHER SURGERY

| | OUR CASES | REFERRED CASES |
|-------------------------------|-----------|----------------|
| Pomeroy sterilization | 21 | 14 |
| Madlener | 4 | 6 |
| Cornual resection | 3 | |
| Myomectomy | 3 | 1 |
| Umbilical hernia | 2 | |
| Uterine polyp | 1 | |
| Repair bladder | 1 | |
| Repair intestine | 1 | |
| Taking down Coffey suspension | 1 | |
| Salpingo-oöphorectomy, right | | 1 |
| Salpingo-oöphorectomy, left | | 1 |

pital under close observation for several weeks, provided hemorrhage did not drive us to active interference.

Eclampsia, Pre-Eclampsia, Toxemia.—A small group (12 patients) of these patients were delivered by cesarean section. We never consider eclampsia and/or pre-eclampsia as an indication for section; rather, we use section in selected cases as the method of terminating the pregnancy, and then only when adequately treated. We prefer section under local anesthesia—at least without inhalation anesthesia—in those patients in whom the cervix is thick, hard, and undilated, or if disproportion exists.

Ninety-three and seven-tenths per cent, or 390, of the 416 sections have been cervical sections; 2.3 per cent, or 10, of the 416 sections have been Porro sections; 2.1 per cent, or 9 cases, of the 416 have been classical; 0.7 per cent, or 3, of the 416 have been Water's extraperitoneal type; 0.2 per cent, or 1, of the 416 has been Smith exclusion type; 0.5 per cent, or 2 cases, have been post-mortem sections; and 0.2 per cent, or 1, of the 416 was full-term ovarian preg-

TABLE III. INDICATIONS

| (Our Cases) | | | |
|--|----|--|----|
| Disproportion | 93 | Previous section | 8 |
| Disproportion and previous section | 53 | Previous section, classical | 2 |
| Disproportion and breech | 13 | Previous section and transverse lie | 1 |
| Disproportion and difficult previous labor | 8 | Previous section and breech | 2 |
| Disproportion and cervical dystocia | 3 | Previous section and toxemia | 1 |
| Disproportion and uterine inertia | 3 | Placenta previa, centralis | 8 |
| Disproportion and face | 3 | Placenta previa, lateralis | 4 |
| Disproportion and placenta previa, lateralis | 3 | Placenta previa, marginalis | 11 |
| Disproportion and placenta previa, marginalis | 2 | Premature separation of placenta | 9 |
| Disproportion and transverse lie | 2 | Breech and uterine inertia | 4 |
| Disproportion and premature separation of Placenta | 1 | Breech and previous stillborn | 1 |
| Disproportion and pre-eclampsia | 1 | Breech and prolonged sterility | 1 |
| Disproportion and rectovaginal fistula | 1 | Breech and subluxation of pubis | 1 |
| Disproportion and tuberculous pelvic bone | 1 | Breech and cervical dystocia | 1 |
| Fibroids | 4 | Shoulder presentation | 1 |
| Face | 3 | Transverse lie | 1 |
| Repaired 3d degree laceration | 3 | Elective | 1 |
| Elderly primipara | 3 | Male pelvis (endocrine) | 1 |
| Pre-eclampsia | 3 | Prolapsed cord | 1 |
| Double uterus | 2 | Repaired vesicovaginal fistula | 1 |
| Malformed pelvic inlet | 2 | Myocarditis mitral stenosis | 1 |
| Cervical dystocia | 2 | Eclampsia | 1 |
| Stenosis cervix post-radium | 1 | Stenosis of cervix | 1 |
| (Referred Cases) | | | |
| Disproportion | 44 | Placenta previa, centralis | 7 |
| Disproportion and previous cesarean section | 15 | Placenta previa, marginalis | 5 |
| Disproportion and previous difficult labor | 9 | Placenta previa, lateralis | 2 |
| Disproportion and Breech | 4 | Placenta and to sterilize | 1 |
| Disproportion and eclampsia | 2 | Premature separation of placenta | 6 |
| Disproportion and uterine inertia | 2 | Previous section | 3 |
| Disproportion and elderly primipara | 2 | Previous section and impending rupture | 2 |
| Disproportional and marginal placenta previa | 2 | Previous section and nephritic toxemia | 1 |
| Disproportion and toxemia | 1 | Transverse lie | 6 |
| Disproportion and prolapsed cord | 1 | Eclampsia | 3 |
| | | Pre-eclampsia | 1 |
| | | Pre-eclampsia and P.O. cervical stenosis | 1 |
| | | Pre-eclampsia and breech | 1 |
| | | Pre-eclampsia and uterine inertia | 1 |
| Face | 2 | Pelvic kidney | 1 |
| Fibroids | 2 | Failure of head to engage | 1 |
| Cervical dystocia | 2 | Encephalitis and sterilization | 1 |
| Breech and pelvic tumor | 1 | Carcinoma cervix | 1 |
| Nephritic toxemia | 1 | Multiple sclerosis and fibroids | 1 |
| Double uterus | 1 | Diabetes | 1 |
| Ovarian tumor and bleeding vagina | 1 | Anencephalic | 1 |
| Ovarian pregnancy at term | 1 | Elective, twins | 1 |

Condensed Indications

| | OUR CASES | REFERRED CASES |
|-------------------|-----------|----------------|
| Disproportion | 138 | 73 |
| Previous section | 67 | 21 |
| Placenta previa | 28 | 17 |
| Abruptio placenta | 10 | 6 |
| Breech | 8 | 0 |
| Fibroids | 4 | 2 |
| Toxemia | 4 | 8 |
| Cervical dystocia | 4 | 2 |
| Vaginal repairs | 4 | 0 |
| Elderly primipara | 3 | 0 |
| Miscellaneous | 5 | 12 |
| | 275 | 141 |

TABLE IX. FETAL DEATHS—STILLBORN AND PREMATURE

| YEAR | OUR CASES | | | REFERRED CASES | | |
|------|-------------|--|---------------|--------------------|--|-------------|
| | FETAL DEATH | OBSTETRIC INDICATION | SECTION | FETAL DEATH | OBSTETRIC INDICATION | SECTION |
| 1935 | Still-born | Premature separation of placenta. Full term | Porro | | | |
| | Premature | Placenta previa, central; 8 months; 4 lbs.; lived 3 days | Beck | | | |
| 1936 | | | | Premature 24 weeks | Right ovarian tumor; ruptured membranes | Beck |
| | | | | Premature | Nephritic toxemia 7 months 1 week; 3 lbs. 1 oz.; died in 4 hours | Munro-Kerr |
| | | | | Premature | Placenta previa, central; 7½ months; died premature; 2 lbs. 14 oz. | Beck |
| 1937 | Premature | Myocarditis mitral stenosis; lived 10 hours; 3 lbs. 6 oz., atelectasis, patent foramen ovale | Munro-Kerr | Still-born | Premature separation of placenta; full term | Munro-Kerr |
| | Premature | Placenta previa, marginal; 8 months | Beck | | | |
| 1938 | Premature | Central placenta previa; 6½ months; weight not given | Beck | | | |
| | Premature | Central placenta previa; 6 months | Low Classical | | | |
| 1939 | | | | Still-born | Premature separation of placenta; 8 months | Porro |
| | | | | Still-born | Eclampsia; 8 months | Post mortem |
| 1940 | | | | | | |
| 1941 | | | | Still-born | Premature separation of placenta; pre-eclampsia; full term | Munro-Kerr |
| | | | | Full term | Transverse lie and fibroids; died, atelectasis | Porro |
| | | | | Premature | Placenta previa, central; 7 months; lived 12 hours | Beck |
| 1942 | | | | | | |
| 1943 | Still-born | Premature separation of placenta; 8½ months | Munro-Kerr | Still-born | Hydrops of baby; 7½ months; fetal erythroblastosis | Munro-Kerr |
| | Still-born | Premature separation of placenta; 8 months | Munro-Kerr | Premature | Eclampsia and pre-eclampsia; 6 months; lived 4 hours | Beck |
| | | | | Premature | Placenta previa; marginal; 7 months circulatory collapse; 3 lbs. ½ oz. | Munro-Kerr |

nancy. Actually, both Water's and Smith sections are cervical in type so that 394 of the 416 sections, or 94.5 per cent, were cervical.

In addition to the sections, we also did a minimal amount of other surgery (see chart), chief of which was for sterilization. The Pomeroy type was used thirty-five times, the Madlener ten times, and cornual resection three times, giving a total of forty-eight sterilizations, or 11.5 per cent.

Morbidity.—Using the standard morbidity requirements of the American College of Surgeons, there were 36 of our cases, or 13.1 per cent, morbid, and 21 of the referred cases, or 14.6 per cent, morbid.

TABLE VII. TRIAL LABOR

| | | |
|----------------|----|-------|
| Our cases | 58 | 21.1% |
| Referred cases | 32 | 22.3% |
| Total | 90 | 21.5% |

TABLE VIII. MORBIDITY

| | OUR CASES | REFERRED CASES |
|--|-----------|----------------|
| Postoperative reaction: | 14 | 3 |
| Postoperative reaction and transfusion | 1 | 1 |
| Postoperative reaction and pyelitis | 1 | |
| Postoperative reaction and anemia | 1 | |
| Postoperative reaction and sapremia | 2 | |
| Pyelitis (one with anemia) | | 5 |
| Mastitis (one with anemia) | | 2 |
| Hemorrhage (with anemia) | | 1 |
| Anemia and transfusion | 1 | |
| Pneumonia | 1 | |
| Mastitis | 2 | |
| Mastitis pneumonitis and sulfonamides | 1 | |
| Pyelitis | 4 | |
| Sapremia | 3 | 3 |
| Sapremia and mastitis | 1 | |
| Sapremia and pyelitis | 1 | 1 |
| Sapremia and retained lochia | | 1 |
| Sapremia and transfusion | | 1 |
| Thrombophlebitis: Iliofemoral | | 1 |
| Acute phlebitis | | 1 |
| Acute cystitis and syphilis | | 1 |
| Anemia | 1 | |
| Total | 36 | 21 |
| Percentages | 13.1% | 14.6% |

Fetal Mortality.—In the Personal group of 275 sections we lost sixteen babies, which is 5.8 per cent, an uncorrected fetal mortality. Twelve were neonatal deaths, and four stillborn. It is interesting to note that eleven of the sixteen babies were lost because of placenta previa or premature separation of the placenta.

In the referred group of 141 sections we lost 20 babies, or an uncorrected fetal mortality of 14 per cent. Thirteen were neonatal deaths and seven were stillborn. Here again we note that nine of the twenty babies were lost because of hemorrhage in the mother. Twenty of the thirty-six fetal deaths were due to either placenta previa or premature separation of the placenta. There were eleven full-term babies lost in the thirty-six deaths; six were in our cases and five in the referred group. The uncorrected fetal mortality of 36 deaths in 416 sections is 8.6 per cent.

Discussion of Maternal Mortality.—In 3,935 deliveries during this twelve-year period we had nine maternal deaths, six were cesarean section deaths,

TABLE XI. FETAL DEATHS, REFERRED CASES (1935 TO 1946)

| | |
|----------------------------------|----------|
| <i>Stillborn Premature</i> | |
| Erythroblastosis fetalis | 1 |
| Anencephalic | 2 |
| <i>Stillborn Term</i> | |
| Premature separation of placenta | 3 |
| Eclampsia | 1 |
| <i>Premature</i> | |
| Placenta previa | 6 |
| Ovarian tumor in mother | 1 |
| Nephritic toxemia | 1 |
| Eclampsia | 1 |
| Carcinoma cervix | 1 |
| Impending rupture of uterus | 1 |
| Erythroblastosis fetalis | 1 |
| <i>Full Term</i> | |
| Atelectasis | 1 |
| | <hr/> 20 |

TABLE XII. INFANT MORTALITY IN 416 SECTIONS (1935 TO 1946)

| | PERSONAL | PER CENT | REFERRED | PER CENT | TOTAL | PER CENT |
|-----------------|----------|----------|----------|----------|-------|----------|
| Neonatal Deaths | | | | | | |
| Premature | 9 | | 12 | | 21 | 5.00 |
| Term | 3 | | 1 | | 4 | 0.96 |
| Total | 12 | 4.4 | 13 | 9.1 | 25 | 6.00 |
| Stillborn | | | | | | |
| Premature | 1 | | 3 | | 4 | 0.90 |
| Term | 3 | | 4 | | 7 | 1.70 |
| Total | 4 | 1.4 | 7 | 4.9 | 11 | 2.60 |
| Total | 16 | 5.8 | 20 | 14.0 | 36 | 8.60 |

The six cesarean deaths are reported as follows:

CASE 1.—A. L. B., December, 1937; referred case; para i.

Indication: Eclampsia and pre-eclampsia treated four days. Two medical consultants.

Type of Section: Munro-Kerr low flap.

Baby: 3 lbs. 8 oz. Lived.

Death in twenty-four hours, severe toxemia. No prenatal care.

CASE 2.—L. J., January, 1937; referred case; para iii.

Indication: Premature separation of placenta. Pre-eclamptic.

Type of Section: Munro-Kerr low flap.

Baby: Dead in uterus.

Death in five hours after section, of hemorrhage and toxemia. No prenatal care.

CASE 3.—E. T., December, 1938; our case; para iv; weight 245 pounds.

Indication: Three previous difficult forceps deliveries; contracted pelvis; treated pre-eclampsia; in labor several hours.

Type of Section: Beck low flap.

Baby: Lived.

Death on eighth day, of sepsis, acute suppurative endometritis; peritonitis; miliary abscesses. Good prenatal care.

TABLE IX—CONT'D

| YEAR | OUR CASES | | | REFERRED CASES | | |
|------|-------------|---|------------|----------------|--|------------|
| | FETAL DEATH | OBSTETRIC INDICATION | SECTION | FETAL DEATH | OBSTETRIC INDICATION | SECTION |
| 1944 | Full term | Disproportion and previous section; congenital absence of esophagus; 6 lbs. 5 oz. | Munro-Kerr | Premature | Placenta previa, lateral; 7½ months; 4 lbs. 6 oz.; lived 8 hours | Munro-Kerr |
| | Full term | Disproportion; died first day; 5 lbs. 4 oz. | Munro-Kerr | Still-born | Anencephalic; placenta previa | Munro-Kerr |
| | Premature | Placenta previa; central; 7 months; 3 lbs. 10 oz. | Classical | | | |
| | Still-born | Premature placenta previa; central; 6 months | Munro-Kerr | | | |
| 1945 | Premature | Placenta previa, marginal; 7½ months; died 3rd day; 3 lbs. 3 oz. | Munro-Kerr | Premature | Carcinoma cervix; 6½ months | Classical |
| | Full term | Cervical dystocia; cerebral injury; 5 lbs. 12 oz. | Munro-Kerr | Premature | Impending rupture of uterus; 8 months | Munro-Kerr |
| | Premature | Double uterus; 6½ months; died in several hours | Classical | Premature | Hydrops; fetal erythroblastosis; 6½ months | Beck |
| | | | | Premature | Placenta previa, marginal; 6½ months; 2 lbs. 7 oz. | Munro-Kerr |
| 1946 | Premature | Premature separation of placenta; 6 months; lived 12 hours | Beck | Still-born | Anencephalic; 7 months | Munro-Kerr |

TABLE X. FETAL DEATHS, OUR CASES (1935 TO 1946)

| | |
|----------------------------------|----|
| <i>Stillborn Premature</i> | |
| Placenta previa | 1 |
| <i>Stillborn Term</i> | |
| Premature separation of placenta | 3 |
| <i>Premature</i> | |
| Placenta previa | 6 |
| Premature separation of placenta | 1 |
| Double uterus | 1 |
| Myocarditis in mother | 1 |
| <i>Full Term</i> | |
| Congenital absence of esophagus | 1 |
| Cerebral injury | 1 |
| Cause not recorded | 1 |
| | 16 |

and three were noncesarean section deaths. Of the nine deaths, two were in our personal group and seven were in the referred group. In the six cesarean deaths four were in the referred group. There were two deaths in our personal group and both were cesarean deaths.

The cesarean deaths include two postmortem sections which we include in this report for completeness of review, but actually we feel they have little to offer to the study.

deaths per 1,000 live births. We have had no maternal deaths in personal or referred cases since 1942. We are not optimistic enough to think we will not have other deaths. We report this study with no sense of superiority but *rather* offer it to further develop the following ideas:

1. Cesarean sections per se are not the chief cause of maternal deaths that they are thought to be, but rather it is the obstetric complications in most cases that cause death; this applies in general to the fetus.

2. Obstetric patients who are cared for by proper prenatal study and individualization definitely reduce maternal and fetal mortality.

3. Evidence is herewith provided to show that cesarean section is increasing in usefulness, scope, and frequency, and the study as shown justifies it.

4. The study shows the preponderance of cervical sections as compared with all other types. The percentage of extraperitoneal sections is low because we attempt to avoid obstructed labors and resort to section before potential or known infection exists. In our hands, as of present writing, the cervical or low-flap section has fulfilled our needs more satisfactorily than any other type of section. The results justify it.

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CASE 4.—J. M. B., July, 1939; referred case; para iii.

Indication: Pre-eclampsia; breech; difficult first labor.

Type of Section: Post mortem. Patient treated for one week before section; transfused (hemoglobin 52 per cent) and digitalized. Cyclopropane anesthesia started by new anesthetist (without approval).

Baby: Lived.

Death: Acute dilatation of heart failure. No prenatal care.

CASE 5.—E. C., May, 1939; referred case; para ii.

Indication: Patient in convulsions on admission. No time to institute treatment.

Type of Section: Postmortem done in bed immediately after she died in convulsions.

Baby: Dead. No prenatal care.

CASE 6.—R. L., 1942; our case, para i.

Indication: Disproportion.

Type of Section: Munro-Kerr low flap.

Baby: Lived.

Death: Pulmonary embolism four hours after section. Good prenatal care.

The first mortality in our personal group was due to sepsis, and overwhelming infection which killed the patient in eight days. It occurred in 1938 before the advent of sulfonamides, penicillin, or other antibiotics which we commonly employ today. The second mortality in our group was due to pulmonary embolism, which we feel is a surgical risk faced by any patient undergoing surgery. In the referred group all four deaths had no prenatal care and were seen by us after the emergency existed. The four deaths were primarily pre-eclamptic or eclamptic, although one died secondarily of hemorrhage.

TABLE XIII. MATERNAL DEATHS IN 416 SECTIONS (1935 TO 1946)

| | TOTAL CASES | DEATHS | PER CENT |
|----------------|-------------|--------|----------|
| Personal cases | 275 | 2 | 0.72 |
| Referred cases | 141 | 4 | 2.80 |
| | 416 | 6 | 1.44 |

TABLE XIV. MATERNAL DEATHS IN 3,935 DELIVERIES (1935 TO 1946)

| | DEATHS | PER CENT |
|-----------------------|--------|----------|
| <i>Personal Cases</i> | | |
| Cesarean | 2 | |
| Noncesarean | 0 | .053 |
| <i>Referred Cases</i> | | |
| Cesarean | 4 | |
| Noncesarean | 3 | .175 |
| Total | 9 | .225 |

We realize that the mortality in both mothers and babies in our group are low, due to good luck in some cases, of course, but not unlike the results obtained by many obstetricians who follow a plan of careful study to fit the needs of each case. The maternal mortality in our personal group is far below the maternal mortality for the State of Virginia in 1946, which is 2.2 maternal

crystals are dusted in the uterine cavity, especially around the cervix and the incision; 5 Gm. are dusted under the flap; and 5 Gm. are dusted over the line of sutures in the flap and in the lower part of peritoneal cavity. A total 15 Gm. is administered. We have had only thirty cases in which this plan of treatment has been used, but feel that this is a sufficient number for a preliminary report.

TABLE I

| CASE NO. | HOURS IN LABOR | HOURS MEMBRANES RUPTURED | TEMPERATURE AFTER 72 HOURS | INFANT MORBIDITY | INDICATIONS FOR SECTION |
|----------|----------------|--------------------------|--|------------------|-----------------------------|
| 1. | 30 | Not ruptured | Normal | Living infant | Cephalopelvic disproportion |
| 2. | 24 | 10 | Normal | Living infant | Cephalopelvic disproportion |
| 3. | 56 | 16 | Normal | Living infant | Cephalopelvic disproportion |
| 4. | 29 | Not ruptured | 1 day | Living infant | Cephalopelvic disproportion |
| 5. | 24 | Not ruptured | Normal | Living infant | Cephalopelvic disproportion |
| 6. | 48 | Not ruptured | Normal | Living infant | Cephalopelvic disproportion |
| 7. | 36 | Not ruptured | Normal | Living infant | Cephalopelvic disproportion |
| 8. | 18 | Not ruptured | Normal | Living infant | Cephalopelvic disproportion |
| 9. | 19 | 19 | 4 days | Living infant | Cephalopelvic disproportion |
| 10. | 18 | 18 | 7 days | Living infant | Cephalopelvic disproportion |
| 11. | 24 | 24 | Normal | Living infant | Cephalopelvic disproportion |
| 12. | 28 | Not ruptured | 4 days | Living infant | Cephalopelvic disproportion |
| 13. | 24 | Not ruptured | 2 days | Living infant | Cephalopelvic disproportion |
| 14. | 36 | 12 | 2 days | Living infant | Cephalopelvic disproportion |
| 15. | 34 | 12 | 2 days | Living infant | Cephalopelvic disproportion |
| 16. | 18 | Not ruptured | 2 days | Living infant | Cephalopelvic disproportion |
| 17. | 35 | 20 | Normal | Living infant | Cephalopelvic disproportion |
| 18. | 72 | 60 | (Mother died 21 hours after operation. Cause of death at autopsy: Pneumonia, no evidence of metastatic infection.) | | |
| 19. | 15 | Not ruptured | Normal | Living infant | Cephalopelvic disproportion |
| 20. | 38 | 22 | Normal | Living infant | Cephalopelvic disproportion |
| 21. | 25 | Not ruptured | 2 days | Living infant | Cephalopelvic disproportion |
| 22. | 36 | 24 | Normal | Living infant | Cephalopelvic disproportion |
| 23. | 30 | 20 | Normal | Living infant | Cephalopelvic disproportion |
| 24. | 36 | 24 | 5 days | Living infant | Cephalopelvic disproportion |
| 25. | 28 | 16 | Normal | Living infant | Cephalopelvic disproportion |
| 26. | 16 | Not ruptured | Normal | Living infant | Cephalopelvic disproportion |
| 27. | 24 | 20 | 4 days | Living infant | Cephalopelvic disproportion |
| 28. | 60 | 26 | 5 days | Living infant | Cephalopelvic disproportion |
| 29. | 84 | 24 | 8 days | Living infant | Cephalopelvic disproportion |
| 30. | 52 | Not ruptured | Normal | Living infant | Cephalopelvic disproportion |

All of these patients were admitted as emergencies, deliveries having been attempted by midwives or physicians. Vaginal examinations had been done on most of them, although a reliable history could not be obtained in each case. Some undoubtedly had had several vaginals, as well as bacon rind to lubricate the passage. This is an old midwives favorite technique.

The shortest labor was fifteen hours and the longest was eighty-four hours. The average length of labor before operation was thirty hours. The membranes had been ruptured in 70 per cent of these cases, the time interval ranging from ten to sixty hours. There were twenty-five primiparas and five multiparas. Anaesthetics used were Ethelene, Cyclopropane, or Nitrous oxide and ether.

Length of stay in the hospital was from ten to twenty-seven days, the average was fourteen days.

Our morbidity was 43 per cent, based on any elevation of temperature above normal after the first seventy-two hours postoperative. There was one case of wound infection. Other causes of morbidity were due to low grade infection. There was no thrombophlebitis, no fistulas, nor serious infections.

CESAREAN SECTION IN POTENTIALLY INFECTED PATIENTS USING SULFATHIAZOLE IN THE UTERUS AND THE PERITONEAL CAVITY*

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IT IS a well-established fact that mortality and morbidity are increased in cesarean sections in direct proportion to the length of labor. Especially is this true when the membranes rupture early. Douglas has shown the reason for this by taking cultures in five-hundred patients at the time of operation. He obtained cultures from the intraovular space and from the cervix. His bacteriologic findings, correlated with the clinical results, clearly show that a section performed prior to the onset of labor is relatively safe, but that after labor has begun, the risk from infection increases definitely and progressively with each hour of labor. This is true even if the membranes are not ruptured. From his work, the bacteriologic figures show that cesarean section should not be done on patients who have been in labor for twelve hours or longer. There have been many types of cesarean sections advocated to deliver living babies when patients were known to be infected or potentially infected. The earliest attempt was the Porro section which began in 1876. Porro amputated the uterus at the cervix, thus removing from the abdominal cavity the infected organ.

In 1907, Frank of Cologne devised a method of extraperitoneal section which was later modified by Latzko. This method has been later modified by Waters and Ricci. Some obstetricians are very enthusiastic in their support of this method. Objections to it advanced by others are:

1. The technical difficulties encountered in the performance of the operation.
2. The possibility of opening the peritoneal cavity, thus defeating the purpose for which the operation is done.
3. The danger of injury to the bladder and ureters.
4. The danger in operating on an infected organ.

In 1941, recognizing these dangers, we endeavored to find a safe method of delivery in potentially infected labor with cephalopelvic disproportion, and began the local use of sulfanamides, attempting to achieve bacteriostasis, if not actual sterilization of the uterus and surrounding organs.

Procedure

The technique we now use, after making a few early changes is: Trans-peritoneal-flap operation, longitudinal incision through the lower uterine segment. After delivery of the products of conception, 5 Gm. of sulfathiazole

*Read at the annual meeting of the South Atlantic Association of Obstetricians and Gynecologists, Savannah, Ga., Feb. 6 to 8, 1947.

ASPIRATION CURETTAGE OF THE ENDOMETRIUM IN A CANCER CLINIC

An Analysis of 200 Cases

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A TUMOR clinic usually has a large number of women in or beyond their fourth decade who present abnormal genital bleeding and/or discharge as their complaint. It is universally conceded that if physical examination fails to disclose an obvious cause for such bleeding or discharge the patient should be subjected to further study, including diagnostic curettage of the endometrium. Accepted practice calls for surgical dilatation of the cervix and curettage of the endometrium under anesthesia in all cases in which carcinoma of the endometrium is a possibility. A safe and efficient procedure, the only factor which precludes this being an ideal diagnostic measure, is the reluctance with which many women of this age group accept hospitalization and even minor operations. The result is procrastination in many instances where early diagnosis is essential.

Aspiration curettage of the endometrium is a procedure involving no anesthesia and no hospitalization. It is promptly accepted by the patient and therefore can be performed at the initial examination. Most gynecologists emphatically state that aspiration curettement should not be used except in the diagnosis of physiologic changes in the endometrium, and a few doubt its value even in so-called functional problems. Israel and Mazer¹ are in the latter group. They subject their patients to surgical dilatation and curettement without hospitalization and usually without anesthesia, although occasionally ethyl chloride inhalation is used. It seems of some significance to us that 47.3 per cent of their patients refused to submit to the procedure for at least three months. Inventors of various devices for aspiration or punch biopsy of the endometrium have usually warned that they were not to be used when carcinoma of the endometrium was a possibility. Novak² does so, but he also states that he can remove the endometrium as completely with his cannula as with the surgical curette, and that he sometimes performs therapeutic curettage with it. Douglas³ reports that in his clinic aspiration is used as a screen and has substantially reduced the number of surgical curettements performed there.

Procedure

At the Steiner Clinic the number of patients with unexplained abnormal bleeding and/or discharge became so large in 1939 that it was absolutely impossible to subject them to hospitalization because of insufficient facilities and

One mother died twenty-three hours after operation from pneumonia: diagnosis confirmed at autopsy. There was no evidence of puerperal infection, peritonitis, or blood-borne infection to the lungs. This was a case in which we erred in giving an inhalation anaesthetic, cyclopropane, and incidentally this represents the only death we have had in the last one hundred twenty-five full-term cesarean sections on our service at Roper. As this patient did not die from puerperal infection, we feel that our mortality for the mothers is zero, and all of the babies lived.

The sulfathiazole blood concentration taken twenty-four hours after operation ran from 5 to 10 mg. per 100 c.c. of blood, therefore we suggest caution when patients have nephritis or marked anemia. If infection should develop, we give sulfonamides, penicillin and blood transfusions.

Repeat sections have been done on two of these patients, one of which had rather dense adhesions.

For the purpose of comparison and to illustrate the hazards of the extra-peritoneal section, we quote a few excerpts from recently published reports. Williamson and Goldblatt, New York. In 25 cases using the Latzko operation. The peritoneal cavity was opened in 33 per cent. Thrombophlebitis occurred in 12 per cent. Wound infection occurred in 12 per cent. Total morbidity, 44 per cent.

Daichman and Pomerance, Brooklyn. In 100 cases using the Waters extra-peritoneal section. The peritoneal cavity was opened in 36 per cent. The bladder was injured in 17 per cent, including 15 per cent with perforations. Vesicoabdominal fistulas 3 per cent, and one of these also had a vesicovaginal fistula. The average hospital stay was fifteen days; the shortest was ten days, the longest was ninety-two days. Many of the patients drained from the lower angle of the drain site for two to four weeks. Ten per cent had definite wound infections.

Waters, New Jersey. Two hundred and fifty cases using the Waters extra-peritoneal technique. Reports bladder perforations in 1.6 per cent. Peritoneal perforations 27 per cent. There were two deaths, and he omits any postoperative morbidity data.

Conclusions

Transperitoneal cesarean section is made reasonably safe in potentially infected cases when sulfathiazole is placed in the uterus and the peritoneal cavity. Our results compare most favorably with the extraperitoneal sections which are being used in the same type patient.

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TABLE I. INITIAL PATHOLOGIC DIAGNOSIS IN ASPIRATION CURETTINGS

| | PRE-MENOPAUSAL | | POST-MENOPAUSAL | | ENTIRE GROUP | |
|------------------------------------|----------------|-------|-----------------|-------|--------------|--------|
| Number of patients | 142 | 71.0% | 58 | 29.0% | 200 | 100.0% |
| Insufficient tissue (QNS) | 15 | 10.5% | 9 | 15.5% | 24 | 12.0% |
| Proliferative | 21 | 14.7% | 3 | 5.1% | 24 | 12.0% |
| Mixed proliferative and secretory | 1 | 0.7% | | | 1 | 0.5% |
| Secretory | 22 | 15.4% | | | 22 | 11.0% |
| Hyperplastic | 61 | 42.7% | 8 | 13.7% | 69 | 34.5% |
| Atrophic | | | 13 | 22.3% | 13 | 6.5% |
| Chronic endometritis, undetermined | 3 | 2.1% | 2 | 3.4% | 5 | 2.5% |
| Chronic endometritis, fibromyoma | 5 | 3.5% | 2 | 3.4% | 7 | 3.5% |
| Chronic endometritis, polyps | 2 | 1.4% | 2 | 3.4% | 4 | 2.0% |
| Chronic endometritis, puerperal | 7 | 4.9% | | | 7 | 3.5% |
| Cervical polyp, precancerous | 1 | 0.7% | 1 | 1.7% | 2 | 1.0% |
| Adenocarcinoma of endometrium | 2 | 1.4% | 16 | 27.5% | 18 | 9.0% |
| Adenoacanthoma of endometrium | | | 1 | 1.7% | 1 | 0.5% |
| Epidermoid carcinoma of cervix | 1 | 0.7% | 1 | 1.7% | 2 | 1.0% |
| Adenocarcinoma of cervix | 1 | 0.7% | | | 1 | 0.5% |

Obviously, the 12 per cent of the entire group in whom the aspiration curettings were reported to contain "quantity of tissue not sufficient for diagnosis" (QNS) and the 6.5 per cent showing only atrophic endometrium were regarded as undiagnosed, and we were almost as reluctant to accept chronic endometritis of undetermined origin as a definite entity, especially in a woman past the menopause. The final diagnoses in these cases, often arrived at only after prolonged observation, are presented in Table II. One of the QNS patients eventually showing hyperplasia had a surgical curettage unknown to us at another hospital seven days before coming to our clinic for the aspiration. Another patient aspirated by the resident (QNS) was surgically curetted by him ten days later and found to have hyperplasia. The same resident aspirated QNS from a patient whom he surgically curetted ten days later, the report being adenocarcinoma of endometrium, grade I. A postmenopausal patient with QNS on repeated aspiration and curettage was observed for fourteen months before carcinoma of the cervix became evident. In one 78-year-old patient with pyometrium, nothing other than a benign stricture of the cervix could be found in three years' observation. One postmenopausal patient with chronic endometritis ceased to bleed after aspiration and has remained well. All patients in whom the final diagnosis was "undetermined" were followed from three to six years without treatment and without return of symptoms and some are still under observation.

TABLE II. FINAL DIAGNOSES IN GROUP WITH "UNSATISFACTORY" ASPIRATION CURETTAGE DIAGNOSES

| | BEFORE MENOPAUSE | AFTER MENOPAUSE | | |
|-----------------------------|---------------------|-----------------|----------|-------------------------|
| | Q N S | Q N S | ATROPHIC | CHRONIC ENDOMETRITIS |
| Atrophic vaginitis | | 2 | 3 | |
| Carcinoma of cervix | 1 | 1 | | |
| Carcinoma of endometrium | | 1 | | |
| Cervical polyp | | | 3 | |
| Estrogen withdrawal | | 1 | | |
| Fibromyomata uteri | 5 | 1 | 4 | |
| Fibrosis uteri | 1 | | | |
| Hyperplasia of endometrium | 2 | | | |
| Arterial hypertension | | 1 | 3 | |
| Stricture of cervix, benign | | | | 1 |
| Diagnosis not determined | 6 | 3 | | 1 |
| Total | 15 | 9 | 13 | 2 |

limited personnel. Rather than attempt to screen such a group with clinical impression and therapeutic trial, it was decided to use aspiration curettement primarily with questionable cases to be subjected to surgery. The instrument used was the author's cannula, not because of any supposed superiority, but because of familiarity with it. It consists merely of a size 12 metal male catheter with a knife edged fenestrum on the convex surface of its shortened beak. It should be emphasized that thorough aspiration curettage of the endometrium does not consist of merely introducing a cannula and haphazardly moving the fenestrum against the mucosa while suction is being applied. After sounding carefully for direction of the canal, dimensions of the cavity and irregularities of its surfaces, the cannula is introduced and the fenestrum applied firmly to one border. Suction is then applied and maintained while the fenestrum is methodically carried over the entire endometrial surface. If the uterus is very movable a tenaculum should be used to steady the cervix. Suction is then discontinued and the instrument withdrawn. The contents of the cannula are then ejected into normal saline solution and the fragments of endometrium are carefully separated from the blood, mucus, etc., to be placed in formalin or Zenker's solution.

Material

The two hundred cases herein analyzed were consecutive and unselected from patients 36 years of age or older, except that neither those diagnosed previous to referral to the clinic nor those aspirated by interns in the first six months of their service were included. Obviously an accurate evaluation of a diagnostic procedure as practically applied to a large group should not include the work of too many novices. The orientation experience of the authors is reflected in this series, however. Only cases followed up adequately for a period of two to six years were included for it is difficult to see how untraced cases could do else than cloud the picture. No morbidity was reported by any of the patients and no untoward bleeding occurred even though their activity was not restricted because of the procedure per se.

Results

The result of this method of diagnostic management of the entire group is shown in Table I. Patients who had experienced a period of amenorrhea of six months or more were judged to be past the menopause (ages 40 to 78 years), while all others, even though they were obviously undergoing the menopause, were placed in the premenopausal group (ages 36 to 57 years). That such an arbitrary separation is practical is reflected in the fact that no atrophic endometrium was found in this latter group, although undoubtedly many of those women had their status obscured by abuse of estrogen therapy, as indicated by the disproportionately large percentage of proliferative and hyperplastic endometria found among them. All of the proliferative endometria and six of the eight hyperplasias in postmenopausal patients were due to estrogen therapy. Two patients in this group with hyperplastic endometrium had granulosa cell tumors of the ovary. The ages of the patients with carcinoma of the endometrium ranged from 43 to 78 years, and this lesion plus malignancies of the upper cervix and ovary accounted for 33.4 per cent of the postmenopausal patients' symptoms of abnormal bleeding or discharge without obvious cause, as contrasted with only 3.5 per cent in the premenopausal group.

Conclusions

In conclusion, although we were impressed with the success attending the use of aspiration curettage as a screen measure in a cancer clinic, it should not be presumed that we recommend it to displace more generally accepted measures. Neither are we in a position to compare it with the efficiency of vaginal smears as a screen in such patients although a study of this kind would be most interesting. We do wish to emphasize that aspiration curettement is a useful procedure in the study of the endometrium if properly applied and properly interpreted. Its chief advantages, (1) immediate acceptance by the patient, and (2) economy, in that neither hospitalization nor anesthesia is required, weigh heavily against objections to its use, either real or theoretical.

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Unfortunately, the exigencies which resulted in this study allowed us to check only 35 cases with tissue obtained at surgical dilatation and curettage or hysterectomy, excluding cases preoperatively irradiated (Table III). This number seems ridiculously small, but it is explained by the fact that we frequently did not burden our pathologist (who was often without the services of a technician during the emergency) with study of surgical curettings at the time radium was applied to patients whose previous biopsies showed cancer, and that practically all corpus carcinoma received preoperative radiation. One-half of the patients with carcinoma of the endometrium in this clinic are inoperable and one-half of the others refuse hysterectomy. It will be noted that "surgical" diagnosis agreed in full with "aspiration" diagnosis in twenty-six cases and partly agreed in two cases, a total of 80 per cent agreement. Surgical diagnosis disagreed positively with aspiration only twice: (1) a patient whose aspiration curettings were reported QNS was found to have carcinoma of the endometrium at curettage ten days later, (2) another aspirated QNS was found to have hyperplasia at curettage fourteen days later (all work in both cases by the resident). Surgical diagnosis disagreed with aspiration findings *negatively* in that QNS reports on curettage specimens followed aspiration diagnoses in one case each of adenocarcinoma of endometrium grade I, hyperplasia of endometrium, atrophic endometrium, proliferative endometrium, and chronic endometritis. In partial disagreement, (1) a 51-year-old patient, four years postmenopausal, whose aspiration showed "atrophic endometrium with polyps" at laparotomy fourteen days later was found to have "proliferative endometrium with polyps" and a fresh corpus hemorrhagicum was found in one ovary! (2) aspiration in a patient, aged 45 years, revealed "chronic endometritis" while curettage three days later showed "chronic endometritis with polyps."

TABLE III. ASPIRATION DIAGNOSES CHECKED BY "SURGICAL" DIAGNOSES

| | |
|--|----|
| Surgical diagnosis in full agreement | 26 |
| Surgical diagnosis in partial agreement | 2 |
| Surgical diagnosis in positive disagreement | 2 |
| Surgical diagnosis in negative disagreement | 5 |
| Total cases checked without preoperative radiation | 35 |

Comment

Undoubtedly many will look askance at the small number of hysterectomies in the presence of such a large number of patients with hyperplasia of the endometrium in the premenopausal group. We are of the opinion that many of those women were showing the result of estrogen therapy for menopausal phenomena. It should be remembered that stilbestrol was introduced on the market shortly before the beginning of this study. We regard spontaneous hyperplasia of the endometrium with irregular bleeding at menopausal age as a clinical entity, and have always preferred to treat it with x-radiation unless coexisting lesions made surgery desirable. We have no quarrel with the routine hysterectomist who at least can have the advantage of complete detailed pathologic study of the uterus to counterbalance his small but irreducible operative mortality. On the other hand, like Miller,⁴ we do not admit that adequate management of irregular bleeding or discharge from the upper genital tract of women who have completed their families calls for hysterectomy in every case. It is our hope to make the sixty-one patients with endometrial hyperplasia the subject of restudy in the future.

Consequently, if we can develop a clinical picture, easily recognizable, we shall have benefited both the patient and satisfaction in the practice of medicine. If we can decrease the unintentional abuse of estrogens, we shall both enhance their properly selected use and diminish the hazards of excessive estrogen therapy. Furthermore, we will clarify indications for compensatory therapy and will thereby appropriately alleviate complaints.

As stated, the coincidence of certain symptoms and signs suggest a "hyperestrin syndrome." Like most clinical syndromes, all features may vary in obvious intensity or degree—and individual symptoms or signs may be absent in a given case. The symptoms and signs may be presented as chief complaints. Or they may be determined by questions and examination.

From a review of records made in private practice, the following symptoms and signs are offered for consideration under a classification which may be designated, "hyperestrin syndrome":

1. *Premenstrual nervous and emotional irritability*.—Characteristically, this state is cyclic in its occurrence prior to menstruation and in its partial or total relief with the establishment of free menstrual flow. Patients complain that they feel nervous, depressed, tense. Some patients have used the word "ornery." Some feel apprehensive. Duration of such irritability is often two to five days, and not infrequently seven to ten days before menstruation. The degree of irritability may be mild to severe, even to a sense of incipient insanity. Sometimes, it is the husband who observes his cyclic inaptitude.

2. *Premenstrual or menstrual headache*.—This symptom is inconstant, variable, and not much help as a differentiating feature, because of the frequent occurrence of headaches from other causes, including hypoestrinism. However, the hyperestrin headache is often migraine in type, not relieved by ordinary doses of sedatives, and usually not relieved by gynergen. Frequently, such headache is frontal and suboccipital and is associated with:

3. "*Allergic rhinitis*" of a sort.—Subjectively, the patient may report persistently recurrent annoyance or distress after repeatedly ineffective therapy for the condition. She may complain merely of recurrent nasal "stuffiness" and may or may not complain of postnasal drip. The gynecologist usually learns of the condition incidentally, since it is not considered related to his field of work. Objectively, the lower turbinates may appear swollen, pale, or obviously edematous, and a clear, mucous, postnasal drip may be seen by the examiner, simply with the aid of a tongue depressor.

4. *Premenstrual hypersensitiveness of the breasts*, plus a "shotlike" or nodular consistency of the mammary substance.—This is a most common and typical symptom and sign. The symptom varies from the patient's sense of increased heaviness to actual soreness, occurring two to five or even ten days before menstruation. The patient may complain that her breasts are too sore for touch, even by her brassiere. On examination, the texture of the mammary substance is more significant than gross size of the breasts. The hyperestrin type is shotlike to nodular consistency, due to alveolar development. A woman with good estrin-progesterone balance has breasts whose consistency is smooth and not tender. A further distinction may be made from the relatively smooth, cordlike firmness of ductal proliferation. In long-standing, severe cases of hyperestrinism, we see the finer, shotlike or nodular breast developed to the degree, called chronic cystic mastitis, or Schimmelbusch's disease. After treat-

HYPERESTRINISM IN PRIVATE PRACTICE*

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WE ALL have witnessed the dramatic relief of menopausal hot flushes after estrogen therapy. We have watched estrogenic rejuvenation of the atrophic vaginal mucosa, even years after menopause. Most of us have seen the lactating breast dry up rapidly with doses of stilbesterol which were formerly considered to be large. More recently, certain workers are reporting beneficial effects in selected cases wherein truly massive doses of stilbesterol are administered. We are convinced of the clinical efficacy of estrogens in a variety of clinical conditions.

However, *estrogenic therapy aggravates the complaints of certain patients*. One may reasonably suspect that such complaints may be caused by an already overabundant supply of estrogens. Because of such cases, this paper will suggest a group of symptoms and signs, so frequently occurring together that they may be considered to constitute a "hyperestrin syndrome." If there is such a clear-cut picture as a clinically obvious hyperestrin syndrome, its recognition will stop the abuse of estrogens and will indicate a rational approach to the alleviation of refractory complaints which are too often treated with estrogens.

The advantages of endometrial biopsies, of cytologic scrapings, and of biochemical assays with regard to estrin-progesterone effects are not available to the average medical practitioner. If such procedures were more readily available, the average patient cannot economically afford them. Furthermore, the average patient is very average. She does not have theca cell tumors nor other spectacular anomalies.

Articles in lay magazines have exalted estrogen as the panacea for female ills. And a large volume of the medical literature is little better. Too often, if the patient does not ask for estrogens, the doctor orders such therapy—very often as a "shot in the dark," when he does not know what else to do. Again, too often, his nurse gives the "shots" of estrogen indefinitely and without further supervision. When the estrogen aggravates rather than improves symptoms, the doctor and his patient may wonder why.

Without endowed laboratory and research facilities, the average doctor in private practice must depend on the patient's story and on his own clinical observations. Both the history and physical examination must be routine, and therapeutic indications must be obvious. The average doctor has neither the time nor the inclination to delve deeply nor to ponder patiently in matters which are debated among research workers.

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Comment

Since the primary purpose of this paper is the presentation of a hyperestrin syndrome, as such, only brief additional comment will be made:

1. The medical literature is so extensive with respect to estrogens that no attempt is herein made to give due credits. The contribution of this paper, if any, is its organization. The literature since 1940 has been reviewed by the Library Service of the American College of Surgeons in preparation for this paper. Apparently no similar presentation of a hyperestrin syndrome has been made in the American literature. However, after the substance of this paper was completed, a single reference of a similar conception was found in the French medical literature in which similar features were incorporated under the term, "hyperfolliculinism," (Bernard, A.: "Digestive disturbances due to excessive secretion of folliculin" (Translated Title) *Arch. d. mal. de l'app. digestif*, 34: 56-61, 1945.)

2. The etiology of clinical hyperestrinism appears to be due either to excessive estrin production or to a relative hyperestrinism due to deficient progesterone production. Excessive estrin production appears to be due to abnormal ovarian stimulation with incomplete maturity and development of single or multiple follicular cysts. Such may be due to chronic pelvic congestion (meaning vascular engorgement, stasis, and edema) from retroverted uteri, prolapsed ovaries, vaginitis, endocervicitis, incompleting sexual stimulation, emotional and debilitated states. Abnormal stimulation of primordial follicles by toxic products from a vaginitis or endocervicitis via the lymphatics seems logical and understandable. Such cause and effect is apparently seen frequently all through menstrual life, and subsequently to menopause. The relative hyperestrinism due to hypoprogesteronism is most often seen in the menopausal age due to failure to corpus luteum formation.

A discussion of therapy would doubtless be as controversial as the features of hyperestrinism itself. Obviously, the etiologic factor should be eliminated. General hygiene, tonics, elimination of vaginal and cervical infection, relief of pelvic congestion by hot douches to improve pelvic circulation are primary therapeutic considerations.

Although massive doses of estrinogens may give certain relief by inhibiting pituitary function, it seems to the writer more logical not to give more estrin in hyperestrinism. Frequently the pituitary would seem to be already too much inhibited.

Of the hormones, thyroid in small doses except in actual hyperthyroid patients, seems to be well accepted and beneficial in selected cases, particularly in the generally exhausted type of individual. Progesterone to supplement estrin or testosterone, perhaps to antagonize estrin, are certainly beneficial orally or by hypo in small or larger doses in many patients. In chronic cystic mastitis, a combination of anterior pituitary-like hormone with methyl testosterone alleviates many cases. Recently, reports indicate the need for thiamine by the liver to inactivate excessive estrin concentrations. And there is some

ment and regression of two such cases of the writer, removal of residual cysts showed them to be the "blue dome cysts" of Bloodgood. Others have reported similar relationship.

5. Menstruation is primarily characterized by the usual occurrence of clots and by usually profuse flow.—The menstrual cycle may be short, normal, long, regular or irregular. It is not the purpose of this paper to explain such inconsistency. However, in hyperestrinism the prolongation or shortening of the menstrual cycle may well be due to pituitary inhibition and variable inhibition of ovulation and of corpus luteum development.

6. *Libido* is often low or absent.—However, it may be quite normal. The glans clitoridis may be normal in size and sensitiveness. But more often the glans clitoridis is hyposensitive or completely indifferent and may be as small as a grain of rice. One patient who responded satisfactorily to treatment stated that the clitoridis previously was just as neutrally indifferent as her shoulder. Coitus may be normally satisfactory. Very often it is an indifferent passive accommodation. And not infrequently in simple hyperestrinism without demonstrable pathology, coitus may be extremely distasteful or painful, due to vaginal hyperesthesia.

7. *Pelvic findings* are variable.—But uncomfortable hyperesthesia and some degree of pelvic congestion or edema are usual. Hyperestrinism may be associated with pelvic pathology, such as vaginitis or endocervicitis, which may account for part of the hyperesthesia. But quite as often without apparent pelvic pathology, the hyperesthetic vaginal mucosa appears to be healthy and normal. In marked hyperestrinism, the vaginal mucosa is extraordinarily lush, grayish pink, translucent, clean but moist with deep rugae. The uterus may be small or large normal size but seems more than normally tender. (Note: The examiner must be gentle or else he will learn very little.) The ovaries seem to be within the range of large normal but on careful palpation the surface is nodular, due to immaturely developed follicular cysts, each of which is probably producing estrin. Of course, pathology makes the picture seem more obvious. The pathology may explain the etiology of hyperestrinism. Obviously vaginitis, endocervicitis, cystic cervix, prolapsed or grossly cystic ovary, retroverted or fibroid uterus are conditions which must be considered and dealt with appropriately. Proper treatment of a grossly pathologic entity in the pelvis may improve or correct the hyperestrinism, or it may not. The patient must be considered as a whole and should be treated as a whole to induce her maximum well-being.

If the examiner will regularly look through his microscope at fresh, wet, saline preparations from the vagina, such as those routinely made for trichomonas, he will gain a helpful familiarity with the unstained appearance of vaginal epithelium. Such microscopic observation may require only a minute of time. During that minute, the doctor or his technician may gain an impression of the estrinogen influence on the vaginal epithelium. (Note: The writer first learned of this useful observation from Greenblatt speaking before this association.)

Without time consuming stains and study, the fresh saline suspension from vaginal swab shows the hyperestrinogenic type of vaginal epithelium which are large, distended by a coarsely granular (due to glycogen) cytoplasm with large nucleus. This contrasts with the atrophic (hypoestrin) small vaginal epithelium with concave sides, relatively hyaline cytoplasm, and small or no nucleus. Observations of these contrasting pictures and of intermediate effects may be helpful in completing the clinical picture.

THE EVOLUTION OF OBSTETRICS AND GYNECOLOGY IN THE NEAR EAST*†

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THE Lebanon is a small republic, about the size of Rhode Island, lying between Turkey and Palestine at the eastern end of the Mediterranean. It is less dirty, less ignorant, and less torn with eternal political strife than most of the Orient. The mountains rising to 10,000 feet out of the Mediterranean, topped by the great cedars of Lebanon, carry a mantle of snow six months of the year. It is the only oasis in the hot, dusty Near East. The mountains were refuge for the Crusaders in the twelfth century as they fled before the Saracens after the fall of Jerusalem. The monasteries of the Jesuits and Maronites make up the Christian nucleus left in this Mohammedan world. For nearly one hundred years the *American Medical School* at Beirut has sought to bring American and European medicine to the Orient and break down the prejudices of Moslem and Christian alike. Founded as a mission school and later aided by the Rockefeller Foundation, the school has developed into a teaching institution and hospital equal in equipment and personnel to the average in America. Through its wards pass the advanced obstetric and gynecologic pathology of the Near East. The clinical problems here bear mute testimony to the superstitions, traditional practices, and witch doctoring of the people. To make ward rounds on any day cannot do other than to bring into bold relief the evolution and practice of our specialty through the ages.

Excavations at Nippur indicate the presence of urban life 6000 B.C. The Sumarian, Semite, Babylonian, Assyrian, Chaldean, and Persian civilizations flourished and passed on before the Christian Era. Here, man's mind first questioned, then speculated upon his origin and his destination. Jastrow's translation of the clay tablets from the Library of King Assurbanipal of Assyria contains the earliest references extant to that still dubious question, the prognosis for the outcome of labor. On the altars at Petra, a day's journey by automobile

troughs where the livers of animals were studied to prognosticate the progress and ultimate termination of labor. The liver is still regarded by Arab tribesmen as the seat of the soul. These tablets refer also to fetal monstrosities and what they portended. The anencephalic indicated an era of peace in the land. Anomalies of the ear foretold a long reign for the prince. It is told by Herodotus that the Babylonians provided a couch in the market place where the lying-in woman was brought to receive the counsel of the villagers. In the Souk or

*Read at the annual meeting of the South Atlantic Association of Obstetricians and Gynecologists, Savannah, Ga., Feb. 6 to 8, 1947.

†AUTHOR'S NOTE: Attention is called to the fact that this article deals with the customs and ideas of the uneducated classes. Throughout the Middle East there are thousands of cultured families with enlightened and modern ideas to whom the related facts do not apply.

indication that tocopherol (vitamin E) may be synergistic or otherwise beneficial to estrin-progesterone balance.

In conclusion, if collectively we can determine whether or not there is such an entity as a clinical hyperestrin syndrome and if we can clarify its integrated features, we can determine our individual therapeutic attack. The writer's daily observations strongly support the concept of a hyperestrin syndrome which is practical and applicable in private practice.

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tion at the inlet. A mummy owned by a physician in Cairo, an alumnus of the university, was shown to me in his home one evening after dinner. The woman had died in labor apparently from cephalopelvic dystocia. The pelvis was of the rachitic type and the fetus was in the right occipitoposterior position. This is one of the rare mummies in which the pregnant uterus has been left in situ. Female circumcision, widely used among the early Egyptians, is still practiced among some of the desert tribes of Arabia. The rite is performed at adolescence. Hemorrhage occasionally occurs when the clitoris is cut, and several of these young girls have been admitted to the hospital.

One hundred years after the death of Galen the sword of Islam had cut out an empire extending from Spain to Bagdad, thus providing a cultural medium to catch the torch of Greco-Roman medicine from the hands of the fallen Roman Empire. The military campaigns of Mohammed and his successors were accompanied by much destruction, the most tragic of which was the burning of the great library at Alexandria. Incidentally, the site of this famous center of learning is not known; this is strange, in view of the fact that so many of Egyptian monuments yet stand. In the peace that followed the slaughter, schools, hospitals, and libraries were re-established. Said the first Caliph. "The ink of the doctor is equally valuable with the blood of the martyr." The medical school at Gondisapor in Persia was the first repository of Greco-Roman medicine. Had Arabic medicine done nothing more, this alone would have placed us in her eternal debt. For, while the sword of Christendom suppressed the desire of men to pursue the study of nature's laws, the heathen school at Gondisapor taught and practiced the medicine of Hippocrates. From here Rhazes and Avicenna sipped the cup of knowledge and from their pens came the writings which projected Grecian medicine across the Dark Ages. The school was founded by the Caliph El Welid, and in 707 A.D. a great hospital was established in Bagdad where Rhazes, father of Arabian medicine, practiced and wrote his "El Hawi," a ponderous work covering the whole range of medicine. He recommended craniotomy in dystocia, the linen fillet in obstructed labor, and binding of the legs for the lacerated perineum. He made no reference to puerperal infection, but recognized the association of putrefaction with the disease by selecting the site of the hospital to be built in Bagdad by hanging meat in various parts of the city and where the meat was last to spoil, there he built the hospital. The foundation of this hospital in the northeast suburbs of Bagdad may yet be seen.

A biography of Rhazes written by a contemporary has never been printed, but a hand copy in Arabic script is to be found in the library of Dr. Sami Haddad in Beirut. Here is told the story of him in his old age, how he became blind and calling the eye surgeon to see him, he was about to submit to the operation when he stopped the surgeon and asked him to name the anatomic membranes of the eye. When the surgeon failed to do so, Rhazes dismissed him saying it was better he continue blind than submit himself to the ignorance of a barber surgeon.

Anointing the vulva and vagina with oil to lubricate the birth passage was recommended by him and remains today a universal practice among midwives.

Market Place of Bagdad the public clinic is still held, I am told, where anyone may be invited to advise and prescribe. In one of the remote villages of Syria I saw a parturient woman on a cot in front of her home being attended by relatives and friends, exhortations and prayers being administered vigorously. The Babylonian civilization cultivated a true science in astronomy, but lost the scientific spark when they attempted to read into the stars and their constellations the answers to all questions that perturbed the minds of men. The skylight in the ceiling of many public buildings were studded with stars in constellations. One which can yet be seen in Damascus was used solely for prognosis of sex in the unborn. The astrologist is not unknown in the sickroom today.

What astronomy was to the Chaldean, medicine was to the Egyptian. Imhotep, the first physician, designed the step pyramid of Sakhara at the same time that he was prescribing for sterility in Egyptian women. Sterility is the most frequent gynecologic complaint bringing women to the outpatient department of the University. Under the law of the Koran the Moslem may divorce his wife if she is not pregnant within one year of marriage. Even in the relatively fertile, competition is keen among the wives of the same household. A midwife from Palestine gave me an infallible prescription for sterility: "Mix equal parts of goats' milk and bees' honey, bring to a boil, strain, add some oil of almond, and douche before coitus on the twelfth day from the beginning of menstruation." The first part of the prescription is lifted almost verbatim from the Kahun Papyrus about 2000 B.C. The turpentine stupe, not yet extinct in this country, is widely used in the Near East to hasten labor. A bowl of turpentine is placed beneath the midwife's stool and a charcoal burner placed under it, the fumes passing up and into the vagina. I have heard serious complaints from the man of the household about this procedure, the turpentine fumes contaminating the water pipe which he smokes continuously during the course of labor. The use of turpentine in labor can certainly be traced to early Egyptian medicine. The Ibis Papyrus, 1550 B.C., suggested the burning of turpentine resin on the abdomen to hasten labor. This remarkable medical work also prescribes an early test for pregnancy and after the passage of 5000 years still finds a place in practice of the present. "Pound a watermelon with milk of a woman who has borne a son. Give the patient to drink. If she vomits, she is pregnant; if she have flatulence, she is sterile." A Syrian woman told me she had used this prescription many times and in her experience it had never failed in its accuracy.

Obstructed labor brings many women to the hospital after days of futile efforts to deliver at home. It is inconceivable that a woman could survive five, six, seven days of labor and repeated attempts at delivery, but such cases are frequently seen. Vesicovaginal and rectovaginal fistula from pressure necrosis are the rule in such cases, and repair of these fistula presents a problem in surgical judgment to tax the ingenuity of the most audacious. One case of sigmoid vaginal fistula was seen last year. This unquestionably resulted from compression of the sigmoid between the fetal head and pelvic brim. This woman gave a history of intermittent labor over a period of eight days with frequent attempts at delivery. The rachitic pelvis is the most common cause of obstruc-

obtain permission. The patient's home was many miles from Beirut and the resident assured the husband that transportation of the body without first removing the viscera might result in dire consequences. There was a similar case, he told the relatives, in which removal of the infected organs had not been permitted and during the journey homeward, the gas generated from the infection and the jostling of the body over the rough, hot roads resulted in an explosion which had disseminated parts of the body and the vehicle with its occupants over the Syrian desert. Permission was obtained. Transportation of dead bodies in the Near East is accompanied by many difficulties. In order to transport a body across the borders, it must be hermetically sealed in a special casket as prescribed by the law of the country. This is an expensive operation and so, the family often seeing that death is inevitable, removes the patient in a moribund state from the hospital in order to avoid this expense. It is not unusual to have patients in the last stages of their illness lifted onto the back seat of a Ford touring car and hustled out of the hospital gates.

The practice of gynecology suffers from the prejudices engendered by Islamic teachings regarding the place of women in society. Many Mohammedans refuse permission to their wives' admission to the hospital. Under the law of the Koran the husband should be present when the doctor examines his wife. Consequently, the home delivery service under the supervision of the midwives forms an important part of the obstetric teaching service. The medical students accompany the midwives and are allowed to observe deliveries. Many serious obstetric complications are managed in the home. On one occasion an eclamptic was seen in her home and, according to records kept by the medical student in attendance, the patient is known to have had 49 convulsions before permission was granted to admit her to the hospital. After admission three convulsions occurred, these were controlled by intravenous magnesium sulfate, and the patient recovered following spontaneous delivery of stillborn twins. In the villages the obstetrician when called in consultation by a midwife must often operate under a sheet.

It must be remembered that women of the East enjoy practically no personal freedom. Their living quarters are separate from those of the male, the windows are barred, the doors to the "hareem" from which we get the word "harem" are heavily bolted, and the master of the household takes the key with him when he leaves in the morning. However, the women manage to keep up with male activities by a specially constructed grill between their apartments and the living room of the males. This was impressed on me one evening when, after holding a clinic in Aleppo, I dined at the home of a wealthy Aleppo physician. Of course no women were in evidence. During a sumptuous and elaborate dinner which consumed half the night, I indulged myself to the extent of three large onions. They have an onion, grown only in the Aleppo district, about the size and consistency of an apple, which has a delicate and delicious flavor. The next morning we were to have a clinic in Bagdad and a British army plane flew us the 500-mile journey. Coming into the hotel dining room for breakfast I found in front of my plate another of these onions. The women

and must be one of the contributing factors to the high incidence of puerpera; sepsis seen on the wards of the University Hospital. The Beta hemolytic streptococcus, Welsh bacillus, and colon bacillus bring many patients to the wards. One patient was admitted last year with a huge hematoma invading the labia, perineum, and vaginal walls, the result of too vigorous lubrication. The birth stool advocated by Rhazes is still used in the villages of the East, and there are some obstetricians of experience who insist that the sitting posture facilitates the mechanism of labor. Unquestionably, the high incidence of vesicovaginal, rectovaginal fistula, and third degree lacerations of the perineum seeking surgical relief at the hospital can be traced to the use of the delivery or midwives' stool as recommended by Rhazes.

Avicenna, the prince of Arabic physicians, was born in Khorassan. With a precocious intellect he mastered the Koran at the age of 10 years. He led a roving life among the courts of the East, was imprisoned for taking liberties with the Sultan's harem, and escaped to Ispahan where he spent fourteen years in research and writing. Having led a licentious life, he died at 58 years, spending his last days with the Koran after selling his library and distributing his money to the poor. Osler refers to him as one of the great in medicine. His real and indeed his only contribution was divorcing medicine from Oriental magic. This was his great achievement and for six centuries his teachings dominated the medical schools of Asia and Europe. There are some who credit him with the invention of the obstetric forceps because in his canons of medicine appeared the following paragraph: "In extraction he may bind the head about with a border of cord and draw it carefully with repeated tractions. If that does not bring it on, forceps may be used." Most authors believe, however, that Avicenna applied the forceps and hooks only to the dead fetus. From his writings evolved a practice seen today in the distant Arabian provinces of packing the puerperal vagina with salt. This is recommended as prophylaxis against "putrefaction" and to shrink tissues back to their original size. This practice brings patients to the hospital seeking relief from atresia of the vagina, the stenosis often being so great that in many cases only a pinpoint canal is seen replacing the vagina. The hot cautery was recommended by Hippocrates and was endorsed by Avicenna. Multiple punctures over painful areas were recommended. One patient long in labor was seen last year with a uteroabdominal wall fistula from which amniotic fluid was escaping, the cautery having penetrated a bit too deeply.

It would be natural to assume that Arabic medicine should have acquired much anatomic knowledge because of the frequency with which human dissection was done in Egypt for the purpose of embalming. Such is not the case, however. Removal of the viscera after death was relegated to a low caste, and their observations were never recorded. Mohammed dealt the final blow to human dissection when he declared the dead body unclean and forbade the touching of it with bare hands. Permission for autopsy today is usually obtained by subterfuge. The resident staff at the hospital utilizes methods which might be considered somewhat unethical in America. On one occasion a patient dying of peritonitis presented many interesting features which made us anxious to

Original Communications

DYSMENORRHEA AND OVULATION: CORRELATION OF THE EFFECT OF ESTROGEN THERAPY ON PAIN, THE ENDOMETRIUM, AND THE BASAL BODY TEMPERATURE*

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A MULTIPLICITY of theories makes it plain that the etiology of functional dysmenorrhea remains an unsolved problem. A great variety of treatments which at best give 60 to 70 per cent satisfactory results in the hands of their staunchest advocates also shows that no one of them strikes at the basic, underlying factor. Furthermore, it is not clear by what mechanism relief, when it occurs, is actually accomplished.

One of the most striking characteristics of functional dysmenorrhea is its invariable correlation with a progestational endometrium^{1, 2} or an ovulatory type of basal temperature curve.³ On this basis it has been concluded that ovulation is a prerequisite for dysmenorrhea, and treatment aimed at the suppression of ovulation has been undertaken.^{1, 4, 5, 6} Two to 12 injections of estrogen at intervals ranging from one to ten days were used. In one series² as many as 77 per cent of the treated cycles was pain-free. This injectional therapy, however, often disturbed normal menstrual rhythm. Oral therapy with diethylstilbestrol^{5, 7} and ethinyl estradiol⁶ also has been used with similar results. To our knowledge, no one has attempted to correlate response to therapy with various dosage levels of estrogen. All workers concur in the necessity for starting therapy well in advance of the time of expected ovulation, and for continuing treatment approximately twenty days. It is advised usually that treatment be omitted every third cycle to insure adequate endometrial regression. Some investigators claim^{2, 5} that partial improvement persists after the discontinuation of therapy, but others feel that this treatment has no effect whatever on subsequent cycles, being merely temporary, preventive therapy.⁶ All agree that treatment does not impair subsequent fertility.

*Part of the expenses of these studies was defrayed by a grant to one of us (E.C.H.) by Ayerst, McKenna & Harrison, Ltd., whose products diethylstilbestrol (estrobene) and conjugated estrogens (premarin) were used.

of the household had seen my apparent enjoyment of them and had sent one by special carrier to Bagdad.

These women are remarkable in many ways. They are keen students of poetry and the feminine arts. They make practically all of the famous oriental rugs, and the designs are copied from the gardens as seen from their windows. Such magazines as *Harper's Bazaar* and *Mademoiselle* are not unknown to them, however, and beneath the black veil and black kaffiye they are often dressed in the most modern Parisian or New York fashions.

Sex morality is high among the Moslem women; virginity is an absolute prerequisite for marriage. The hymen is sacrosanct. Special religious courts are in constant session on cases of doubtful virginity. Doctors are constantly being called to testify for or against the integrity of the hymen. An elaborate ritual is set up for the marriage night. I was invited to the wedding feast at the villa of a wealthy man outside of Bierut. An elaborate feast was served by the host and his sons, the guest of honor being the bridegroom. Of course no women were present. After the festivities the bridegroom was given the salutations of all present and he left the banquet hall to join his bride in the women's quarter of the house. Perhaps half an hour passed and there appeared at the door the father of the bridegroom holding aloft that all might see a beautifully embroidered piece of linen on which were the telltale spots of bona fide virginity. Brothers are often the self-appointed protectors of their sisters' virginity. A young Moslem girl gave birth out of wedlock in the American Hospital last year and was attacked by her brother as she emerged from the hospital after bearing her child. This strict sex morality and sex isolation engender a high incidence of perversion in both sexes. It is a major problem in the Near East.

All of these problems are being met, and slowly but surely will be overcome by the teaching at the American University. Another impetus to scientific medicine is coming from the new Hospital and Medical School at Jerusalem. Just how far this will go depends upon political trends, but the American school stands out as a beacon light, carrying scientific enlightenment to a people who for 5,000 years have known little and cared less for the better things of life.

The various schedules of treatment which have been used in this group of patients are outlined in Fig. 1. Patients treated within the last few years received oral therapy exclusively; this was given from the fifth to the fifteenth, or from the fifth to the twenty-fifth days of the cycle. Diethylstilbestrol or conjugated estrogens, chiefly estrone sulfate (premarin) was used. The total cycle dosage varied from 5 to 60 mg. of diethylstilbestrol and from 6.25 to 75 mg. of premarin.

Most of the patients had received antispasmodics, placebos, and other medications without benefit. The oral estrogenic therapy was administered under circumstances in which the psychotherapeutic factor, intentional or otherwise, was held to a minimum, especially as several members of the staff maintained a skeptical attitude toward the possible benefits of treatment.

Results

Correlation of Ovulation and Dysmenorrhea.—

1. *Biopsies:* There was a total of 82 endometrial biopsies of 26 patients. Each patient had one or more baseline biopsies before the institution of treatment. Additional biopsies after untreated cycles were obtained from time to time. In the 50 baseline or untreated cycles, 46 biopsies showed progestational, and 4 showed estrogenic endometriums. All progestational endometriums were associated with dysmenorrhea. In those dysmenorrheic women in whom an estrogenic endometrium was encountered, no pain was present during that particular cycle. A dramatic example of this is afforded by one patient of this series. Biopsies at the termination of seven consecutive untreated cycles were as follows: progestational, estrogenic, estrogenic, progestational, estrogenic, progestational, progestational. Severe dysmenorrhea accompanied each progestational period, whereas bleeding from an estrogenic endometrium was invariably pain-free.

Of 32 biopsies taken at the end of treatment, 21 were progestational and 11 were estrogenic. Pain was associated with 20 of the 21 progestational periods; all of the 11 estrogenic cycles were pain-free. The single pain-free ovulatory period occurred from a very early progestational endometrium.

Although we have made no distinction between various degrees of pain, it is interesting to note that pain was very slight during three cycles in which the endometrium showed minimal progestational change. No attempt was made to correlate the severity of pain and the degree of progestational development, but the impression was obtained that a correlation possibly might exist.

In a previous publication from this department,⁵ it was concluded that there was no constant relationship between the presence or absence of dysmenorrhea and the type of endometrium from which bleeding occurred. The original biopsies of this previous study were re-examined independently by us. All three of us, including one of the authors of the original paper (E. C. H.), found that some of the biopsies previously read as estrogenic showed progestational elements. For this reason, the biopsy readings were correlated again with the clinical histories and the revised correlations agreed with the present observations.

2. *Temperature records:* The studies of several investigators^{9, 10} have shown conclusively that an ovulatory type of basal temperature curve is associated with a progestational endometrium and, therefore, with an ovulatory cycle. In view of this, we have studied patients with dysmenorrhea by basal temperature records as well as by biopsies. Temperature records were obtained from five patients of this study; there was a total of 11 cycles recorded. Five of these cycles showed an ovulatory rise and were associated with pain; six showed an anovulatory type of curve and were pain-free.

Materials and Methods

Our material consists of 54 unselected patients of whom 16 have been reported previously.⁵ These 16 patients, and 8 others, furnished only baseline data of untreated cycles. The effects of treatment were studied during 178 cycles of 30 patients. The correlation of dysmenorrhea and ovulation was studied by endometrial biopsies and basal temperature records. Eighty-two biopsies were obtained from 26 patients, and 11 temperature records were obtained from 5 patients. Biopsies were taken within eighteen hours after the onset of bleeding and were read independently by each of us. Daily rectal temperatures were kept in a manner described elsewhere by one of us.⁵

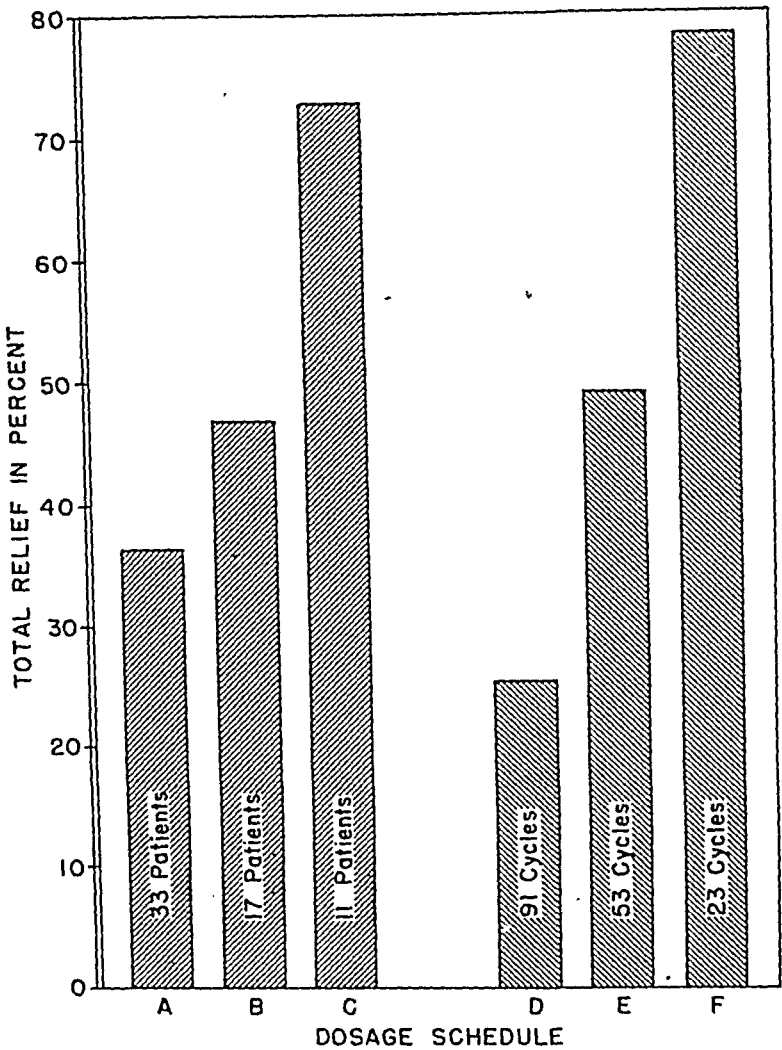


Fig. 1.—The effectiveness of various total dosages of estrogen:
A) less than 25 mg. of premarin or 20 mg. of diethylstilbesterol.
B) 25 mg. of premarin or 20 mg. of diethylstilbesterol.
C) 50 to 75 mg. of premarin or 40 to 60 mg. of diethylstilbesterol.
D) less than 25 mg. of premarin or 20 mg. of diethylstilbesterol.
E) 25 mg. of premarin or 20 mg. of diethylstilbesterol.
F) 75 mg. of premarin or 60 mg. of diethylstilbesterol.

In the evaluation of data, treatment was considered successful only when there was complete relief of pain. In most instances in which we note failure of treatment, there was partial relief of pain, but the large personal factor which enters into the interpretation of "partial relief" renders these results of questionable value.

with a progesterational endometrium or an ovulatory temperature curve, indicating that therapy had not suppressed ovulation. In the 16 cycles in which treatment was successful, an estrogenic endometrium or a flat temperature curve was encountered 15 times; in one instance a very early progesterational change was present.

Several interesting features are shown by the clinical courses of two patients. Fig. 2 illustrates the temperature curves of one of the patients during cyclic treatment with premarin. During cycle 1 the patient received 2.5 mg. of premarin daily for twenty days. The temperature curve shows an ovulatory rise, and the subsequent period was accompanied by dysmenorrhea, despite a relatively large dosage. The following month the dosage was increased to 3.75 mg. daily for twenty days; cycle 2 shows an anovulatory type of curve, and the subsequent period was pain-free. In Fig. 3 are shown the temperature curves of three consecutive cycles of the other patient, treated each cycle with 2.5 mg. of premarin daily for twenty days. The first and third cycles were entirely pain-free, and the temperature curves were of an anovulatory type. The second cycle was accompanied by dysmenorrhea, and the temperature curve shows evidence of ovulation.

These two patients illustrate clearly the fact that the dosage required for the relief of pain varies with the individual; moreover, it may vary from cycle to cycle of the same patient.

A much smaller dosage has been found adequate in many patients; on the other hand, a dosage of 3.75 mg. for twenty days has failed to relieve pain during some cycles. It is evident, therefore, that treatment must be followed by basal temperature curves or biopsies to establish the optimal dose, which is defined as the minimal amount necessary to suppress ovulation. Treatment should not be considered a failure until it has been shown that the dosage was large enough to suppress ovulation. In those patients, in whom inadequate doses afford partial relief, one may expect total relief from adequate therapy.

Discussion

Evaluation of Estrogenic Therapy.—We have tabulated results according to the number of *patients*, as well as the number of *cycles*, treated. The percentage of cycles in which pain was relieved totally is greater than the number of patients treated successfully, since if the first course of therapy failed, further therapy often was abandoned; whereas, if the first cycle of treatment was successful, therapy often was continued. Others² have evaluated results on the basis of the number of individual cycles. We feel, however, that this might not give a true picture and, therefore, we have evaluated the results in individual patients as well as in individual cycles. Reports indicate that various treatments may afford 60 per cent satisfactory results. Our results are consistently better than those obtained by empiric methods.

In contrast to the findings of others,^{4, 5} our schedule of treatment (from the fifth to the twenty-fifth day of the cycle) has not resulted in gross disturbances of the menstrual rhythm, skipping of periods, or other complications. This is true even when our dosages are much larger than those which usually are advocated. From a considerable experience with cyclic oral estrogen therapy in the treatment of functional disturbances of uterine bleeding, we have found¹¹ no cumulative estrogenic effects when this treatment is followed for long periods of time.

Results of Treatment.—The results of various therapeutic schedules are shown in Fig. 1. Our data were distributed in a manner which did not permit statistically significant comparison between 10- and 20-day schedules of the same dosage. Our impression was, however, that the longer course of therapy yielded more satisfactory results.

A total of 33 patients was treated with a total dose of less than 25 mg. of premarin or of less than 20 mg. of diethylstilbestrol. Twelve, or 36.4 per cent, obtained total relief. With a total dose of 25 mg. of premarin or of 20 mg. of diethylstilbestrol, 8 of 17 patients (47.0 per cent) obtained total relief. With a dose of 50 to 75 mg. of premarin or of 40 to 60 mg. of diethylstilbestrol, 8 of 11 patients (72.7 per cent) obtained total relief. These figures are statistically significant.

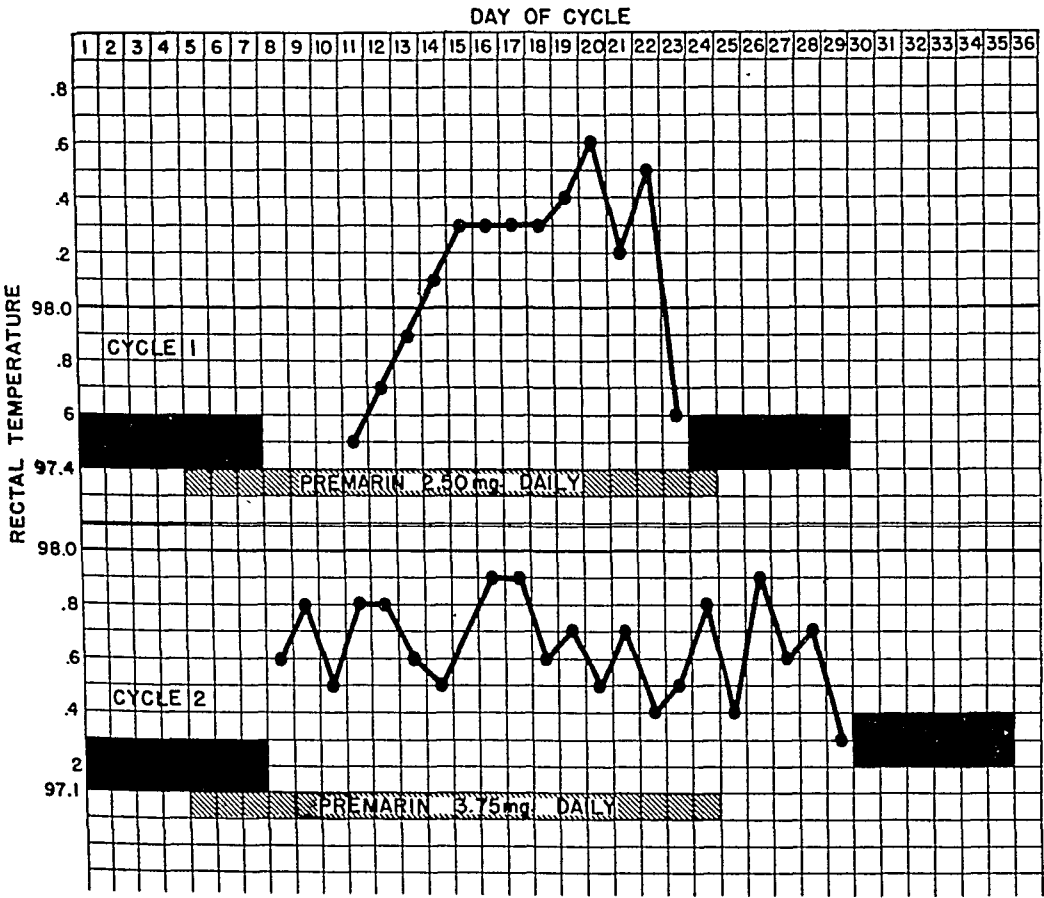


Fig. 2.—Basal body temperature records of a dysmenorrhea patient treated with varied dosages of estrogen.

Ninety-one cycles were treated with doses of less than 25 mg. of premarin or of less than 20 mg. of diethylstilbestrol; of these, 23, or 25.3, per cent were totally relieved. Fifty-three cycles were treated with 25 mg. of premarin or with 20 mg. of diethylstilbestrol; of these 26, or 49.1 per cent, were totally relieved. Twenty-three cycles were treated with 75 mg. of premarin or with 60 mg. of diethylstilbestrol; of these 18, or 78.3 per cent, were totally relieved. These results are statistically significant.

It is obvious, therefore, that the chances of obtaining relief in any cycle or in any individual patient increase as the dose of estrogen is increased.

The Correlation of Therapeutic Response and Ovulation.—These correlations are based on 32 biopsies and 10 temperature records. Treatment failed to provide total relief in 26 of these 42 cycles. All 26 failures were associated

The Role of Progesterone in Dysmenorrhea.—We may discount many of the older theories of functional dysmenorrhea,¹³ since it now seems obvious that progesterone is a prerequisite for its appearance. Whether this action of progesterone depends on its actual presence in the system or results from its effects on various tissues is not definitely established. The latter possibility seems more likely in view of the fact that all demonstrable progesterone has been eliminated from the system^{14, 15} at the time when symptoms are maximal. This time relationship has suggested to some workers that progesterone withdrawal or deprivation may be an etiologic factor in dysmenorrhea. The fact that substitutional doses of progesterone fail to prevent dysmenorrhea¹⁶ negates this theory. Furthermore, we have observed patients with ovarian agenesis in whom dysmenorrhea was produced for the first time by the addition of progesterone to their cyclic estrogen therapy; the dysmenorrhea did not recur when progesterone was discontinued. Injections of large doses of progesterone (25 mg.) during midcycle have been followed within twenty-four to forty-eight hours by dysmenorrhea-like pain.

Cannon⁷ has suggested that dysmenorrhea results from abnormal fragmentation of the progestational endometrium which is associated with overactivity of progesterone. Since injections of progesterone have resulted in dysmenorrhea-like pain in the absence of uterine bleeding, it cannot be fragmentation per se which is responsible for the pain.

There is no evidence which indicates that patients with dysmenorrhea have a physiologic excess of progesterone.¹⁷ So far as we can determine, the tissues affected by progesterone show no undue response. There is no evidence of an estrogen deficiency in dysmenorrhea. Theories that altered progesterone metabolism^{17, 18} may cause dysmenorrhea are based on the supposition that an estrogen deficiency exists, and, therefore, are not substantiated by available evidence.

It has been theorized that dysmenorrhea is the result of vascular spasm.⁵ Estrogens have a parasympathicomimetic (i.e., vasodilator) action. In estrogen deficiency this check on the action of the sympathetic nervous system is decreased with a resultant vasoconstriction, spasm, and pain. There are three main objections to this theory. In the first place, estrogen deficiency has not been proved. In the second place, no relation has been established between vasomotor spasm and dysmenorrhea. In the third place, common vasodilators as nitrites or nicotinic acid neither will relieve nor prevent dysmenorrhea. Dysmenorrhea, furthermore, neither is relieved nor prevented by progesterone, which is known to effect arteriolar dilatation.

The controversial effects of progesterone on the contractility of the uterine musculature are not a factor to be considered, since we feel that abnormal uterine contractility or spasticity plays no part in the pathogenesis of dysmenorrhea. Investigations¹ have shown that the pattern of uterine contractions during the various phases of the cycle is the same for normal and for dysmenorrheic women.

The role of psychogenic factors in functional dysmenorrhea is not minor; in fact, it is the only etiologic factor recognized by some investigators. In one

Cyclic estrogen therapy offers only a temporary prevention of dysmenorrhea, and should not be construed as curative treatment. The temporary sterility induced by adequate treatment does not impair subsequent ovarian function. It is obvious that this method of treatment should not be used in patients in whom pregnancy is desirable.

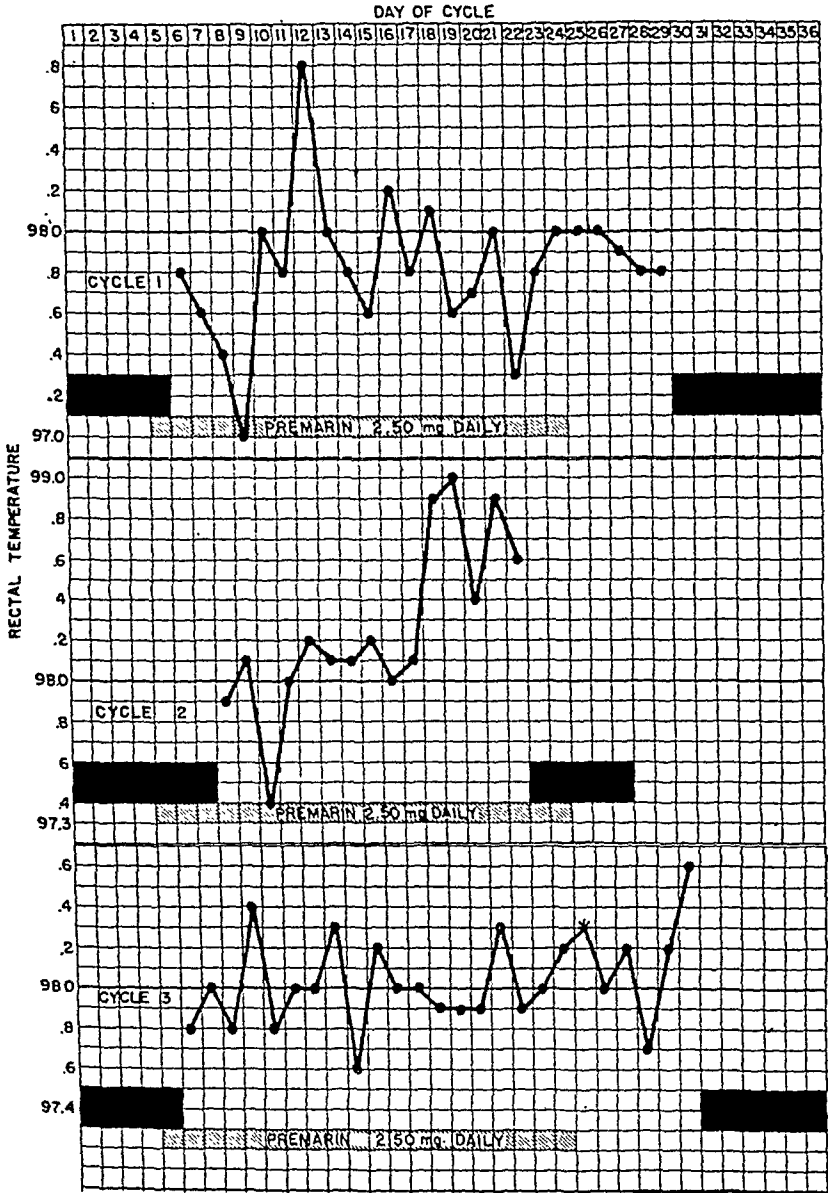


Fig. 3.—Basal body temperature records of a dysmenorrhea patient treated with constant dosages of estrogen.

Suppression of ovulation may be obtained by the use of androgens, and this has been advocated as a treatment of dysmenorrhea. Although doses as large as 900 mg. of testosterone propionate per month have been used,¹² the results are less favorable than those of estrogen therapy. Androgen dosage at this level will cause distressing, and often irreversible, signs of masculinization. In view of the relative dangers as compared to the slight possible benefit of androgen treatment, its use in dysmenorrhea is contraindicated and wholly unjustified.

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of the most recent psychiatric theories,²⁰ dysmenorrhea is considered merely as a symptom complex which is a manifestation of an underlying psychoneurosis. Various phenomena as interstitial edema, basal temperature elevation, increased smooth-muscle sensitivity, and alterations in the status of the breasts, genitals and vasomotor system are the physiologic results of progesterone secretion and, therefore, follow ovulation. The multiple sensory stimuli collectively may reach levels which exceed the lowered threshold of some patients; these patients then interpret the resultant psychic pattern as dysmenorrhea. To the adherents of this theory, treatment with estrogens should constitute a sound, physiologic, therapeutic adjunct to psychiatric treatment, since it eliminates the stimuli which initiate this chain of events.

Summary

1. Fifty-four patients were studied for a total of 228 cycles. Eighty-two biopsies and 11 basal temperature records were obtained.

2. All anovulatory cycles were pain-free. All ovulatory cycles were accompanied by pain save in one instance in which an early progestational endometrium was associated with no pain.

3. Of 33 patients treated with a total dose of less than 25 mg. of premarin or less than 20 mg. of diethylstilbestrol, 12, or 36.4 per cent, obtained total relief. Of 17 patients treated with 25 mg. of premarin or with 20 mg. of diethylstilbestrol, 8, or 47 per cent, obtained total relief. Of 11 patients treated with 50 to 75 mg. of premarin or with 40 to 60 mg. of diethylstilbestrol, 8, or 72.7 per cent, obtained total relief.

4. Of 91 cycles treated with less than 25 mg. of premarin or with 20 mg. of diethylstilbestrol, 23, or 25.3 per cent, were totally pain-free. Of 53 cycles treated with a total dose of 25 mg. of premarin or with 20 mg. of diethylstilbestrol 26, or 49.1 per cent, were totally pain-free. Of 23 cycles treated with 75 mg. of premarin or with 60 mg. of diethylstilbestrol 18, or 78.3 per cent, were totally pain-free.

5. In order to establish the optimal dosage for the individual patient, it is advisable to follow treatment with endometrial biopsies or with basal temperature records.

6. No gross menstrual disturbances followed the described schedule of estrogen administration, although the dosage of some patients was relatively large.

7. The presence either of progesterone or of its physiologic effects is a prerequisite for dysmenorrhea. Although it is initiated by progesterone, other details of the pathogenesis of dysmenorrhea are unknown.

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The Kelly⁷ operation, the more extensive procedure of Kennedy,⁸ and the recently devised Aldridge⁹ operation, as well as many other types of urethroplasty, tend to restore the normal condition of the overstretched urethra, replace the urethra into its normal position beneath the pubic arch, and construct a proper support for the bladder neck and urethra.

W. T. Kennedy,¹⁰ in a recent article, has described the true sphincter of the urethra as composed entirely of circular smooth muscle fibers surrounding the middle and inner thirds of the urethra, together with their associated longitudinal smooth muscle fibers. He suggests that there is a definite anatomic and functional interrelationship between the muscle of micturition and the sphincter of the urethra. This interplay, he claims, results in functional closure of the bladder when the true sphincter retains its circular course, and incontinence will be present in proportion to an elliptical distortion of the true sphincter, and will be permanent if the sphincter is unable to return to its circular form. This distortion is brought about by relaxation of the muscle and (or) periurethral adhesions. He also feels that the levator ani, the bulbo cavernosus, and the transversus perinei muscles aid in the closure of the bladder. He concludes from his anatomic studies that, in order to effect bladder control, it is essential to restore as much as possible all damage inflicted upon the muscular structures and to put the internal meatus of the urethra as far back in the pelvis as possible. By this replacement of the proximal portion of the urethra the relaxation of the muscle of micturition is corrected.

The closure of the bladder is accomplished by the external and internal bladder sphincter aided by the tangential insertion of the urethra into the bladder. The external bladder sphincter consists of striated muscle fibers and is a part of the urogenital diaphragm. The external sphincter is the voluntary sphincter of the bladder. It is our belief, in accordance with the investigations of Von Ludinghausen¹¹ that the internal sphincter, the important bladder closure muscle, consists of two loops of smooth muscle fibers situated at the neck of the bladder, merging with the bladder wall (Fig. 1). The anterior loop is horse-shoe shaped and its fibers encircle the neck of the bladder anteriorly. This loop is open at the posterior urethral wall and its long fibers merge with the longitudinal muscle fibers of the posterior bladder wall. The second loop is also horse-shoe shaped and encircles the neck of the bladder posteriorly. Its long fibers merge with the musculature of the anterior bladder wall. The closure of the bladder is accomplished by the action of the two loops. When the posterior loop contracts, the posterior urethral wall and the bladder neck are tensed and fixed, while the opposing contraction of the anterior loop brings the anterior urethral wall toward the posterior wall, thus accomplishing closure of the bladder.

An analysis of operative procedures used for the cure of stress incontinence involve a common principle. Anatomically they accomplish a thickening and strengthening of the tissues of and around the proximal portion of the urethra and the adjacent trigone of the bladder. This anatomic reconstruction results in a fair percentage of functional restoration. The different operative procedures used achieve a functional result which approaches the normal physiological sphincter mechanism of the bladder.

It is evident that obstetric or surgical injuries affect both the external and internal bladder sphincter. The injury to the internal bladder involves mainly the inferior loop, thus impairing the function of the sphincter muscle. All operative procedures produce a more or less fixed plane at the posterior urethral wall and bladder neck. Thus the undamaged superior loop of the

THE TREATMENT OF URINARY STRESS INCONTINENCE BY THE IMPLANTATION OF A TANTALUM PLATE

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URINARY stress incontinence, whether due to congenital anomalies, intra-partum injury, or surgical trauma, challenges the gynecologist's interest, both from its physiologic and therapeutic aspects.

The causes of urinary stress incontinence are at times difficult to correlate with the anatomic findings found on examination. Generally it can be said that relaxation of the supports of the pelvic organs is often accompanied by urinary stress incontinence.

In a previous study of cases observed in the Gynecological Service of Mount Sinai Hospital¹ it was shown that 37.8 per cent of all cases that required vaginal plastic procedures had urinary stress incontinence. The remaining 62.2 per cent of cases with different degrees of uterine and vaginal prolapse did not have incontinence. This would tend to focus our attention on the sphincter mechanism of the bladder which may be independent, to a certain degree, of uterine and vaginal support.

Azevedo and Campos,² Taylor and Watt,³ and Thomson⁴ claim that changes in the structure of the bladder support show a constant relationship to incontinence. These changes result in loss of angulation of the urethra to the bladder wall, and descent of the posterior wall of the urethra. However, Barnes,⁵ in his studies of urethrograms, does not confirm the above findings, as x-ray studies have not shown a constant relationship of these anatomic changes when incontinence is present. On the other hand, studies of continent women have shown wide variation in urethral angulation. Cystograms studied by Stevens⁶ and others show funneling of the bladder base toward the urethra in urinary stress incontinence.

Apparently there is no close correlation between the anatomic changes in the pelvic floor and the degree of sphincter insufficiency. It is postulated by many workers that the amount of urinary stress incontinence is directly related to the extent of damage to the urethra and the functioning muscles. Yet it is questioned which anatomic alterations are directly responsible for involuntary loss of urine.

The large number of procedures recommended for the cure of urinary stress incontinence is an indication that the results have not been satisfactory. It is often difficult to choose a procedure for the cure of incontinence in a given case, as the degree of evident structural changes may be unrelated to the degree of insufficiency of bladder control. The method first used is usually a simple one and, if it fails, is succeeded by a more complicated operative procedure. These become more extensive with successive failures.

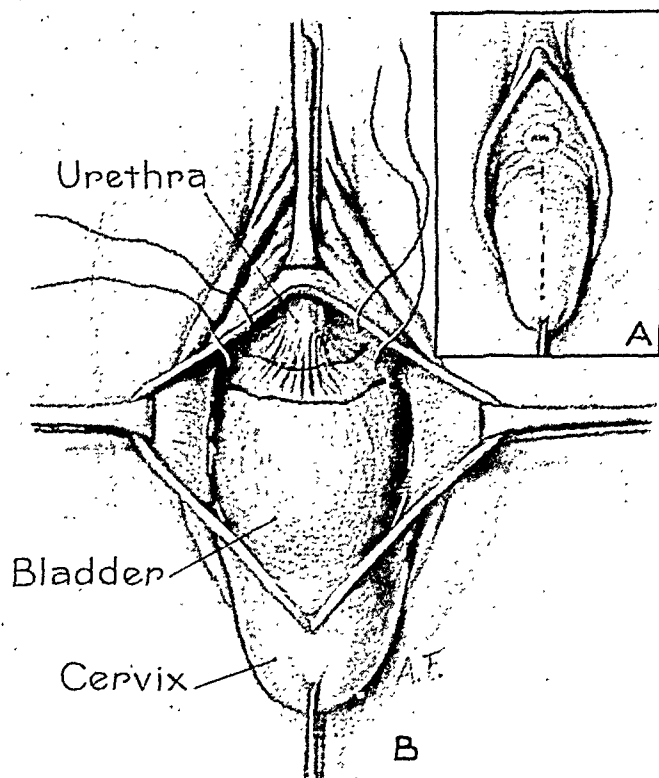


Fig. 2.—*A.* Line of incision in anterior vaginal wall. *B.* Urethra and bladder exposed. Two Kelly sutures placed at bladder neck.

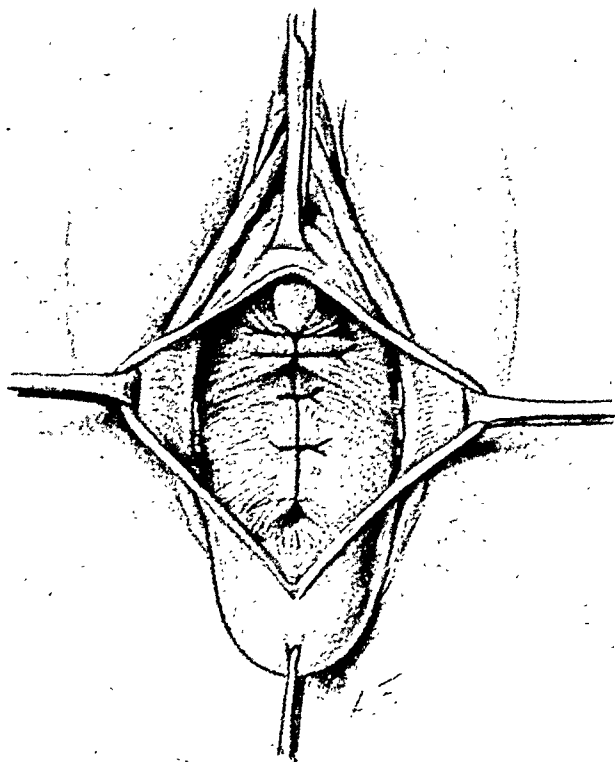


Fig. 3.—Kelly sutures tied and plication of vesicovaginal fascia completed.

internal bladder sphincter is able to approximate the anterior urethral wall against the fixed posterior wall, imitating the normal sphincter mechanism of the bladder.

The disadvantage of all the known operative procedures is that the supportive tissue used for reconstruction may, in the course of time, atrophy or relax, thus depriving the posterior urethral wall of its fixation. This results in imperfect occlusion of the urethra, as the superior sphincter loop cannot sufficiently approximate the anterior urethral wall against the relaxed posterior wall of the urethra.

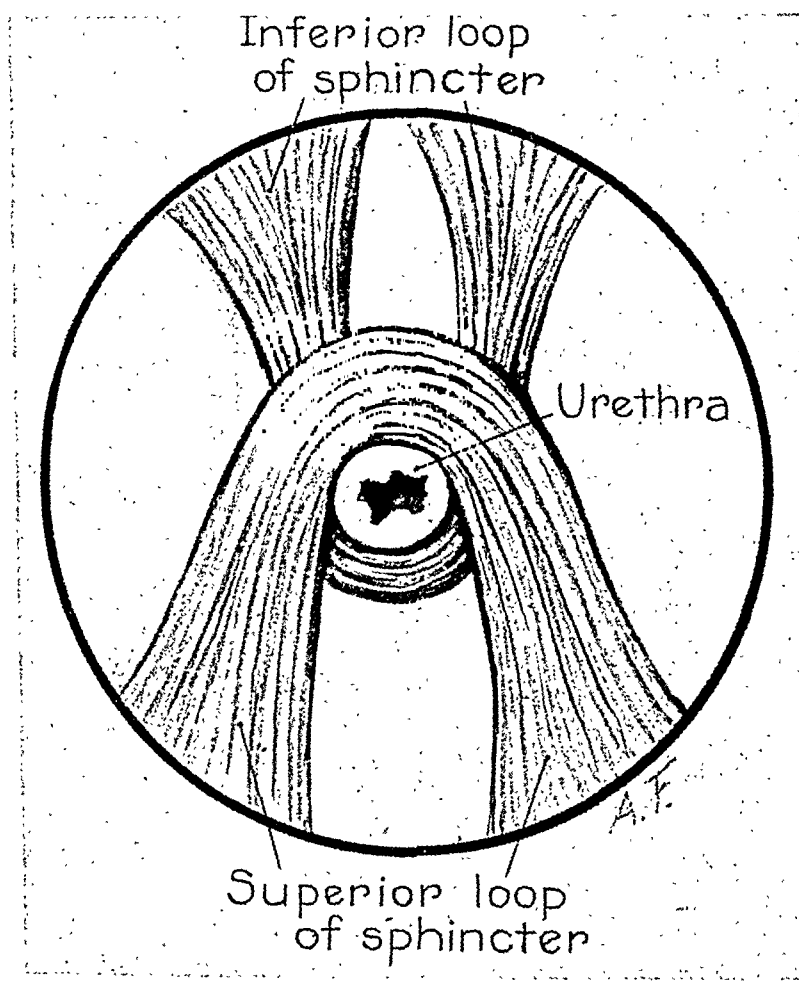


Fig. 1.—The superior and inferior loops of the internal bladder sphincter as demonstrated by Von Ludinghausen.

For many years we have been striving for a method that would accomplish a permanent fixation of the posterior urethral wall and bladder neck. We have tried various methods, utilizing all the known operative procedures, in addition to transplantation of fascial strips, but the results, while generally good, were not entirely satisfactory. We have recently resorted to a plastic procedure by the implantation of a metallic plate beneath the proximal third of the urethra and the urethral vesical junction.

Burke¹² and Burch and Carney¹³ were the first to make surgical use of tantalum. Burke, in 1940, reported his work with tantalum bone sutures and

operation. Four of the patients were operated upon for the first time, while six had had previous operations with failures.

The operative procedure is as follows:

The mucosa of the anterior vaginal wall is incised in the midline starting about 0.5 centimeter from the external urethral meatus and extending to the cervix. The mucosa is reflected by sharp dissection and the bladder, bladder neck, and urethra exposed. The bladder, as well as the urethra, are mobilized so that the index finger can be passed behind the descending rami of the os pubis. The cystocele is repaired by placing two Kelly sutures at the bladder neck and imbricating the vesicovaginal fascia (Figs. 2 and 3). By this procedure the bladder floor is well elevated and the urethra replaced to its normal



Fig. 5.—Preoperative cystogram, on straining, demonstrating marked funneling of the bladder base toward the urethra.

position beneath the pubic arch. A tantalum plate 0.004 inch in thickness and of proper length is then selected and placed beneath the inner third of the urethra and the vesicourethral junction. The position of the tantalum fixation sutures is determined and the plate removed. A tantalum suture 0.015 inch in diameter on a heavy cutting edged needle is then passed through the tissues and periosteum on the inner aspect of the descending rami of the os pubis. When properly placed, these sutures do not have any give on firm traction. The sutures are threaded through previously prepared holes at the ends of the tantalum plate, which is then placed at the vesicourethral junction. The wire sutures are tied firmly and the plate pulled snugly under the urethra and bladder neck, thus producing a permanent fixed plane. The tantalum sutures

plates. He found no clinical or anatomic evidence of bone or soft tissue irritation due to tantalum. In 1942 Pudenz¹⁴ used tantalum clips for hemostasis in neurosurgery. He found that tantalum caused only a minimal fibroplastic proliferation. Later, Pudenz,¹⁵ Fulcher,¹⁶ and Spurling¹⁷ reported on the use of tantalum plates for repair of cranial defects. Since then many reports on the use of tantalum in neuro-, orthopedic and plastic surgery have appeared.

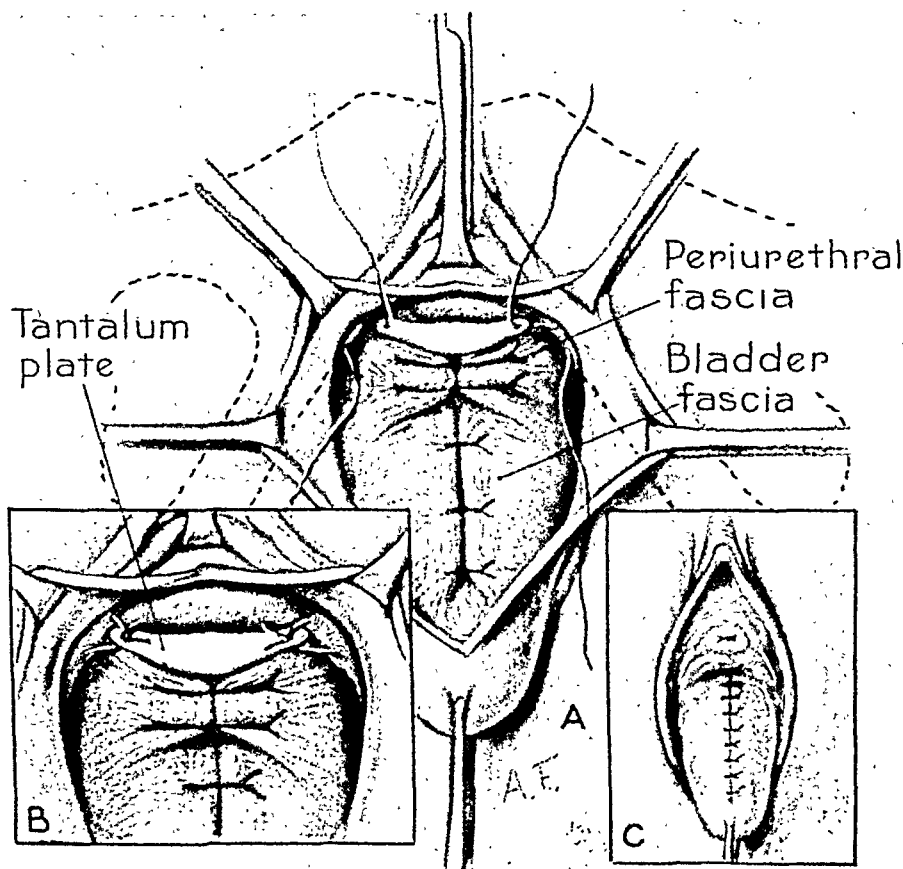


Fig. 4.—A. Tantalum sutures passed through the periosteum on the inner aspect of the descending rami of the os pubis and the tantalum plate in place. B. Tantalum plate fixed at urethrovesical junction by tying the tantalum fixation sutures. C. Vaginal wall closed with interrupted sutures.

We resorted to the use of tantalum because of the sufficient evidence of its inertness in tissues, noncorrosiveness and nonabsorbability. The malleability of tantalum was an additional advantage for our use. Our underlying idea was to permanently strengthen the posterior urethral wall near the bladder junction, thereby restoring a fixed posterior urethral and bladder neck plane against which the intact superior sphincter loop could function satisfactorily. The implantation of the tantalum plate effects a permanent placement of the relaxed proximal third of the urethra and the adjacent bladder wall, far back into the pelvis, thus allowing, according to Kennedy, a complete functional restoration of the relaxed muscle of micturition.

Ten patients with urinary stress incontinence were carefully studied preoperatively by cystoscopic and cystographic examinations, as well as fractional filling of the bladder to determine the degree of bladder control. Only patients with severe stress incontinence were selected for the tantalum plate

nence in any of the ten patients to date. On follow-up examination eight months after operation, the anterior vaginal walls were well elevated, and the plates could not be felt by the examining finger. There have been no complaints of pain or any discomfort on coitus.

Summary

Injury to the urogenital diaphragm results in impairment of the support of the urethra with relaxation and funneling of its proximal portion. This leads to extension of the bladder cavity into the proximal portion of the urethra. The damage to the internal sphincter involves primarily the inferior sphincter loop, while the superior sphincter loop may still function enough to effect some degree of bladder control. Hence, the amount of bladder control that the superior loop can accomplish by its approximation of the anterior to the posterior urethral wall will depend on the degree of saculation of the posterior urethral wall and extent of sphincter damage.

We feel that there is a common anatomic principle involved in all plastic operative procedures devised for the cure of urinary stress incontinence, e.g., replacement of the proximal portion of the urethra beneath the pubic arch, and the formation of a fixed plane at the posterior urethral wall. In this way, the approximation of the anterior toward the posterior wall is made possible, resulting in bladder control.

Relaxation of the fixed plane results in recurrence of stress incontinence. Implantation of a tantalum plate as described, produces a permanent fixed posterior urethral plane, against which approximation of the anterior urethral wall is effected by the contraction of intact superior sphincter loop.

Conclusions

1. Urinary stress incontinence is due to damage to the urethral supports and the sphincter muscles.

2. Injury to the urogenital diaphragm and inferior sphincter loop are the principal causes of urinary stress incontinence.

3. An analysis of the plastic operative procedures is presented.

4. The principle involved for the cure of urinary stress incontinence is common to all of them, e.g., replacement of the sacculated posterior urethral wall and the formation of a fixed posterior urethral plane.

5. Implantation of a tantalum plate produces a permanent fixed posterior urethral plane with good functional results. The simplicity and ease of the operation described merits its use.

6. No ill effects due to foreign body reaction have been observed.

7. Implantation of a tantalum plate has been used successfully in ten cases of urinary stress incontinence.

Addendum

Since this paper was submitted, an additional eight patients with stress incontinence were operated upon with a tantalum plate implantation. Six of these patients had had previous operative procedures for urinary incontinence and two were primary cases with severe degrees of stress incontinence. The results in all these cases have been completely satisfactory.

The follow-up on the ten cases reported in the text is now over one year and all the patients have normal bladder function. There has been no recurrence of urinary incontinence in any case.

are then cut short and the ends turned in against the plate (Fig. 4). The redundant vaginal mucosa is excised and the anterior vaginal wall closed with interrupted No. 0 chromic sutures. If necessary, the operation is completed by a posterior colpoperineoplasty. An indwelling catheter is inserted and the vagina packed with gauze.

In one case, as a test, no imbrication of the urethra was performed. The plate was implanted at the vesicourethral junction and the anterior vaginal wall closed. The functional result in this case was equally as good as in the other nine cases.

It is known that the distance between the pubic rami varies in different patients. Therefore, it is essential to use a plate of proper length to obtain the required urethral fixation and support. The size most frequently used measures $1\frac{1}{8}$ inches in length and $\frac{5}{16}$ of an inch in width.



Fig. 6.—Postoperative cystogram, on straining, demonstrating the tantalum plate in place behind the pubis and the restoration of the normal bladder contour.

The postoperative course of all the patients was uneventful. There was no evidence that the tantalum plate caused any irritation. Six of the ten patients voided spontaneously after the removal of the indwelling catheter. In one case, the patient required repeated catheterization because of the presence of a large amount of residual urine after voiding. All the patients were followed up by cystoscopy, cystography (Figs. 5 and 6), and fractional filling of the bladder, and all had good anatomic and functional results. Examination before discharge on the eleventh or twelfth day revealed healing of the anterior vaginal wall by primary union. In no case was there abnormal residual urine present after voiding. There has been no recurrence of inconti-

LOW SPINAL NUPERCAINE ANESTHESIA IN OBSTETRICS

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THE ideal obstetric analgesic agent is the one which will provide absolute safety for both the fetus and the mother, as well as complete subjective comfort without the undesirable side-effects such as interference with the progress of labor, paralysis of the extremities, drug reactions, and the like. From the standpoint of maximum safety for the fetus, there is no method superior to spinal or caudal analgesia because toxicologic drug reaction and depression are absent, and the trauma resulting from the "bearing down" efforts of the mother is eliminated.

Pitkin and McCormack¹ in 1928 published their "Controllable Spinal Anesthesia in Obstetrics" based on the use of a hyperbaric spinal anesthetic mixture containing 20 mg. of procaine injected into the lower portion of the dural sac to produce a saddle-perineal anesthesia. Lull and Hingson in their book, *Control of Pain in Childbirth*,² reported success with continuous spinal analgesia utilizing minimal doses of metycaine (15 to 22.5 mg. in Ringer's solution) administered in the first or second lumbar interspace. More recently, Adriani and Roman-Vega³ have added glucose to the nupercaine solution to make the mixture hyperbaric, and they control the level of anesthesia by varying the length of time the patient is permitted to remain in a sitting position after injection of the mixture. Parmley and Adriani⁴ have applied this technique to obtain obstetric analgesia and anesthesia.

Pharmacology.—Nupercaine is a complex amine derivative of quinoline. It forms hygroscopic crystals which are colorless, odorless, and tasteless, are readily soluble in water and alcohol, and which form a stable aqueous solution which may be repeatedly boiled without deterioration. *Nupercaine in aqueous solution, however, is precipitated in the form of insoluble base by contact with the slightest amount of alkali.* It is, therefore, advisable to rinse needles and syringes to be used with it with a small amount of nupercaine or weak hydrochloric acid solution, in order to guard against the accidental presence of alkali. Nupercaine has a selective affinity for nervous tissue, paralyzing the peripheral nerves without initial stimulation. Both its potency and toxicity are high, and hence it should be used in a greater dilution and lower total dosage than the other slower acting spinal anesthetic agents. The rapidity with which the anesthesia becomes established varies with the dilution used.⁵ Intrathecal injection of "heavy nupercaine" solution in man usually produces the onset of anesthesia in two to five minutes, although occasionally as long as ten minutes may be required.⁶ The average duration of effective anesthesia is three to four hours, and at times as long as six hours.⁷

Toxicity

The general symptoms of acute nupercaine intoxication are similar to those produced by other anesthetic drugs: initial depression, followed by nervous excitement with loss of coordination, progressing to a stage of clonic convulsions and ultimate death.

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caine was eliminated by using syringes and needles which had been rinsed in weak hydrochloric acid solution prior to autoclave sterilization. Second, great care was taken to have the point of the needle completely intrathecal as partial loss of the nupercaine solution extradurally would contribute to the failure. Third, injection was not made during uterine contraction as the increased spinal fluid pressure establishes a current in the subarachnoid space which may carry the solution upward.

Results

The results of our observations are summarized in Tables I to IX. Evaluation based on subjective relief was necessary since the establishment of a saddle-perineal area of anesthesia did not always mean complete relief of abdominal distress. The patient judged the success of the anesthesia on the basis of her relief from pain and not on the level of the anesthesia. We, therefore, have had to classify as "incompletely relieved" those patients in whom the saddle anesthesia was present but who felt some pain (although diminution of pain was quite marked).

There were three failures in our series. These patients stated that they had absolutely no alleviation of their distress. In two patients, the dose was 1.0 c.c. (2.5 mg.) and in one patient, the dose was 1.4 c.c. (3.5 mg.). The spinal injection was not repeated.

Of the 13 patients listed as "incompletely relieved," 11 had complete perineal anesthesia and marked diminution of abdominal discomfort. The residual distress varied from supra-pubic "sensation" to mild cramping. In 8 of the 11, supplementary anesthesia was unnecessary, but the other three were given inhalation anesthesia at the time of delivery. These three cases are summarized here:

No. 22.—A 21-year-old para ii was given 2.5 mg. of nupercaine in the late first stage, 1 hour, 18 minutes before delivery, resulting in complete perineal anesthesia and diminished pain, but for delivery light cyclopropane anesthesia was necessary. Spinal anesthesia was sufficient for episiotomy and episiorrhaphy.

No. 117.—A 33-year-old para iii was given 2.5 mg. of nupercaine 44 minutes before delivery with resultant complete relief, but as she wanted to be asleep at the time of delivery, she raised a commotion when supplementary anesthesia could not be given in time for the spontaneous delivery. Patient had complete paralysis of the legs.

No. 287.—A 28-year-old para i was given 2.5 mg. of nupercaine 2 hours before delivery with resulting complete perineal anesthesia but residual abdominal pain. Given light cyclopropane anesthesia for delivery, but episiotomy and episiorrhaphy were done under spinal anesthesia alone.

In all 11 patients, the episiotomy and episiorrhaphy were performed under the effect of spinal anesthesia alone.

In the two remaining cases of incomplete relief, the anesthesia effects did not last one hour and supplemental anesthesia was required. The cases are summarized:

No. 118.—A 32-year-old para ii was given 2.5 mg. of nupercaine 3 hours, 50 minutes before and 5.0 mg. 1 hour, 40 minutes before the delivery (both given during first stage). Effect did not last 1 hour and pudendal block was required for the delivery and repair.

No. 353.—A 20-year-old para i was given 2.5 mg. of nupercaine 3 hours, 24 minutes before the delivery, but the spinal anesthesia effect disappeared within 30 minutes. Delivery and episiorrhaphy under cyclopropane anesthesia.

Another case which may be properly included here was the patient who obtained complete relief with initial injection but not with the second injection.

Contraindications

The use of spinal anesthesia is contraindicated in the presence of the following conditions:

1. Diseases of the cerebrospinal system and the spinal column.
2. The presence of pyogenic infection at or adjacent to the prospective site of puncture.
3. Poor condition of the patient, viz., shock, coma, sepsis, and/or severe hypotension.
4. Obstetric complications such as placenta previa, abruptio placenta, fetopelvic disproportion, and high position of the presenting part.
5. Hypersensitivity to the drug.
6. Unfavorable types of patients. (a) Those suffering with chronic backache, headache, or migraine. They may develop an exacerbation or recurrence following the use of spinal injection. (b) Those desiring to be asleep.

Material Studied

Since July 1, 1943, more than 1,500 caudal anesthetics, and since Sept. 6, 1946, 500 low spinal anesthetics have been administered at the three hospitals (Lewis Memorial Maternity Hospital, St. Vincent's Infant and Maternity Hospital, and Mercy Hospital, Chicago) in the obstetric departments under the supervision of Dr. Herbert E. Schmitz. This paper presents the results of our study of 375 cases of low spinal anesthesia at Lewis Memorial Maternity Hospital.

The patients were carefully evaluated as to contraindicating factors (fetopelvic relation, drug sensitivity, etc.), the type of presentation, the station of the presenting part, the cervical dilatation and effacement, and the progress of labor. The "heavy nupercaine" solution was given when delivery was thought to be imminent within the next three hours. The selection of the time was based on our desire to minimize the number of spinal administrations necessary to carry the patient comfortably through the delivery and was dependent on two sets of facts:

1. Perineal anesthesia will usually last for more than three hours, but the abdominal discomfort will recur earlier and may necessitate another injection for relief of abdominal distress.
2. In view of the satisfactory analgesia produced by drugs such as morphine, morphine-scopolamine, demerol, demerol-scopolamine, barbiturates and barbiturates in combination with morphine, demerol, scopolamine, etc., the early first stage of labor may be best treated by such medications and the spinal method reserved for the late first stage and the second stage.

Technique

Before administering any nupercaine as an anesthetic agent the patient was tested for sensitivity to the drug. The test was made by injecting 0.1 to 0.2 c.c. intradermally or by instilling 4 or 5 drops into the nostril.

The nupercaine solution to be used for anesthesia was made hyperbaric by mixing the 1:200 solution of nupercaine with an equal volume of 10 per cent glucose solution. The resulting mixture contained 2.5 mg. of nupercaine per 1 c.c. of 5 per cent glucose solution. This "heavy nupercaine" solution was injected intrathecally at the level of the third or fourth lumbar interspace with the patient sitting up. After thirty seconds, the patient was placed flat on her back but with the head propped up with pillows. The onset of analgesia was usually immediate.

To minimize the chances for failure, the following precautions were observed: First the possible presence of alkali which would precipitate the nuper-

TABLE III. PARITY, PRESENTATIONS AND POSITIONS

| Parity: | | |
|--|----------------|-----------|
| Primiparas—144 | Multiparas—231 | Total—375 |
| Presentations and Positions: | | |
| Cephalic presentations | | 363 |
| Occiput anterior | | 304 |
| OA | 5 | |
| OLA | 168 | |
| ORA | 131 | |
| Occiput transverse | | 17 |
| OLT (Spontaneous rotation) | 2 | |
| OLT (Manual rotation) | 4 | |
| ORT (Manual rotation) | 4 | |
| ORT (Forceps rotation) | 7 | |
| Occiput posterior | | 42 |
| OLP (Spontaneous rotation) | 2 | |
| ORP (Spontaneous rotation) | 5 | |
| OLP (Manual rotation) | 1 | |
| ORP (Manual rotation) | 9 | |
| OLP (Forceps rotation) | 2 | |
| ORP (Forceps rotation) | 9 | |
| OP (Spontaneous rotation) | 1 | |
| OP (Manual rotation) | 1 | |
| OP (Forceps rotation) | 1 | |
| OP (Delivered as such) | 11 | |
| Breech presentations | | 11 |
| SLT (Manual aid) | 1 | |
| SLP (Manual aid) | 1 | |
| SLT (Footling, manual aid) | 2 | |
| SRT (Footling, manual aid) | 1 | |
| SRA (Footling, manual aid) | 2 | |
| SLT (Breech extraction) | 2 | |
| SRT (Breech extraction) | 1 | |
| SRA (Breech extraction) | 1 | |
| Face presentation | | 1 |
| MRT (Bag induction and version and extraction) | | |
| Twins—5 sets | | |

In one of our cases version and extraction was performed in a patient with a face presentation in whom a Voorhees bag had been inserted twelve hours after the rupture of the membranes. Spinal anesthesia was given after the onset of pain and three hours before delivery. The patient was perfectly comfortable, the progressive dilatation of the cervix was easily followed. The Voorhees bag was eventually but gently extruded into the vagina, decompressed, and removed and followed with delivery by version and extraction under supplementary deep ether delivery anesthesia. Perineal anesthesia was complete at the time of delivery.

The duration of subjective relief varied, but the average range was one to two hours. The objective anesthetic effect, however, generally exceeded three hours. The longest anesthetic effect (enough to permit episiorrhaphy) was noted 10 hours after the last injection in one patient and 7 hours, 22 minutes in another.

Untoward Effects

As shown in Table VI, motor weakness to complete paralysis of the lower extremities was present in all of the 375 cases. This is in contrast to the claims of other workers who have reported successful saddle block anesthesia and obstetric analgesia without impairment of the function of the lower extremities.

The effect on the blood pressure is depicted in Tables VI, VII, and VIII. In 221 patients, the difference between the pre- and postinjection reading was less than 10 mm. Hg. Of the 67 patients showing a drop in pressure exceeding 20 mm., only 13 had hypotension requiring the administration of ephedrine. The prophylactic use of ephedrine may prevent the hypotension, but the low

TABLE I. NUMBER OF CASES STUDIED

| | | |
|---|-----|-----|
| Total number of low spinal cases | | 375 |
| Total number with complete subjective relief for at least one hour | | 359 |
| Cases with complete relief with one injection | 328 | |
| Cases with complete relief with two injections | 31 | |
| Cases with complete relief after each of two injections | 23 | |
| Cases with incomplete relief with first but complete after second injection | 5 | |
| Cases with complete relief with first but incomplete with second injection | 3 | |
| Total number of incomplete relief cases | | 13 |
| Cases with incomplete relief after one injection | 12 | |
| Cases with incomplete relief after each of two injections | 1 | |
| Total number of complete failures | | 3 |

No. 259.—A 20-year-old para i was given 2.5 mg. of nupercaine 4 hours, 20 minutes before delivery, and a second 2.5 mg. 1 hour, 10 minutes before delivery. Complete relief followed the initial dose, but the subsequent dose provided only about 75 per cent relief, so that ether was given for the delivery and repair.

For practical purposes, therefore, satisfactory relief (comfortable delivery or alleviation of distress for at least one hour) was obtained in 370 of the 375 patients.

The dosage, the time of administration, and the interval between the time of last injection and the delivery are shown in Table II. The parity, the presentation, and the position are shown in Table III. In Table IV is listed the reasons for the administration of supplementary delivery anesthesia. Table V gives the interval between the time of last spinal injection and the time of the delivery anesthesia. For operative deliveries such as forceps rotation, mid-forceps extraction, breech extraction, and version and extraction, the use of deeper anesthesia is a routine procedure. This is in keeping with the observation of Malpas⁸ of Liverpool during laparotomy and cesarean section that under spinal anesthesia the myometrium of the pregnant uterus exhibits heightened reactivity to various stimuli.

TABLE II. DOSAGE, TIME OF INJECTION, AND INTERVAL BEFORE DELIVERY

| | |
|---|-----|
| Dosage: | |
| Number of cases given 1.0 c.c. per injection | 230 |
| Number of cases given 1.4 c.c. per injection | 118 |
| Number of cases given 2.0 c.c. per injection | 27 |
| | 375 |
| Time of administration: | |
| Stage of labor when spinal anesthesia started: | |
| Stage at initial injection | |
| Late first stage | 275 |
| Second stage | 100 |
| | 375 |
| Stage at subsequent injection | |
| Later first stage | 11 |
| Second stage | 21 |
| | 32 |
| Interval between time of last injection and delivery: | |
| Less than 1 hour | 122 |
| Between 1 hour and 1½ hours | 76 |
| Between 1½ hours and 2 hours | 60 |
| Between 2 hours and 3 hours | 63 |
| More than 3 hours | 54 |
| | 375 |

TABLE VI. UNTOWARD EFFECTS OF SPINAL ANESTHESIA

| | | |
|--|--------|---------|
| Motor weakness to complete paralyses of the legs | | 100.0 % |
| Spinal reactions | 1 case | 0.26% |
| Effects on the blood pressure: | | |
| No change (increase, no change or fall less than 5 mm. Hg) | 148 | 39.5 % |
| Fall between 5 to 10 mm. Hg | 73 | 19.4 % |
| Fall between 10 to 20 mm. Hg | 87 | 23.2 % |
| Fall over 20 mm. Hg | 67 | 17.8 % |
| | 375 | |
| Post-spinal headaches | 52 | 13.8 % |
| Foot drop | 1 | 0.26% |
| Retained placenta (not due to spinal anesthesia) | 1 | 0.26% |

TABLE VII. ANALYSES OF CASES WITH BLOOD PRESSURE FALL OVER 20 MM. HG

| | |
|-------------------------------|----|
| Cases not requiring ephedrine | 54 |
| Cases requiring ephedrine | 13 |
| | 67 |

TABLE VIII. ANALYSES OF CASES WITH BLOOD PRESSURE FALL BELOW 100 MM. SYSTOLIC PRESSURE

| | |
|---|----|
| Fall to level between 100 to 90 mm. Hg. | 19 |
| Fall to level between 90 to 80 mm. Hg. | 15 |
| Fall to level less than 80 mm. Hg. | 3 |
| | 37 |

TABLE IX. OCCURRENCE OF POSTSPINAL HEADACHES

| | |
|-----------------|----|
| Day of delivery | 3 |
| After 12 hours | 9 |
| After 24 hours | 8 |
| Third day | 14 |
| Fourth day | 12 |
| Fifth day | 4 |
| Sixth day | 2 |
| | 52 |

Of the so-called "reactions," there were two. In one, the reaction was later proved to be attributable to demerol sensitivity, but in the other the spinal anesthetic agent was the cause. The cases are summarized.

No. 79.—A 25-year-old para ii was given 100 mg. of demerol 30 minutes preceding the spinal injection. At the time of the spinal anesthesia administration, the patient's pallor was noted, but passed over as insignificant. Thirty minutes later, she was found pale and covered with cold perspiration, with a hypotension of 75/55. She was treated with ephedrine with good response. Demerol sensitivity was suspected on the basis of the pallor preceding the spinal injection, and hence skin test was made which resulted in the development of erythema and urticaria at the injection site of the demerol but not at that of the nupercaine or the control saline solution.

No. 47.—A 26-year-old para iii was given 2.5 mg. of nupercaine at the late first stage (2¼ hours before delivery). The patient developed pallor, bradycardia to 50-60/min., hypotension of 80/0, and irregular fetal heart tones, but claimed no vertigo, dizziness, difficulties, etc. She was given 25 mg. of ephedrine, oxygen, and later 1 c.c. of coramine. Improved in 10 minutes. Obstetric analgesia and anesthesia were complete.

TABLE IV. ANALYSES OF THE 375 CASES

| | | |
|--|----|-----|
| Cases delivered solely under the effect of spinal anesthesia | | 315 |
| Cases requiring supplementary anesthesia for second stage | | 60 |
| Very light (for psychological reasons only) | 10 | |
| Prophylactic deeper anesthesia for operative maneuvers | 1 | |
| Forceps rotations | 2 | |
| Midforceps delivery | 1 | |
| Breech extraction | 6 | |
| Version and extraction | 2 | |
| Anesthesia to supplement waning spinal effect | | 33 |
| Where only "whiffs" of gas or ether required | 6 | |
| For delivery only, repair under spinal effect | 10 | |
| Failure to give second spinal injection | 9 | |
| Failure to give third spinal injection | 3 | |
| Contraindications to subsequent injections: | | |
| Drug reaction (later found to be due to demerol sensitivity) | 1 | |
| Febrile course | 1 | |
| Incomplete relief after second injection | 3 | |
| To supplement incomplete spinal effect | | 3 |
| Complete failure | | 3 |

incidence of hypotension requiring stimulation (0.34 per cent here) and the ready response evoked by the ephedrine when used indicate that therapeutic rather than routine prophylactic administration of ephedrine should be practiced.

Fetal bradycardia may accompany the sudden hypotension resulting from spinal anesthesia and signify fetal anoxemia. Administration of oxygen to the mother promptly corrects the fetal bradycardia.

TABLE V. TIME OF SUPPLEMENTARY ANESTHESIA

| | | |
|--|---|----|
| Number of cases requiring supplementary anesthesia in deliveries occurring: | | |
| Within one hour after the last injection | | 5 |
| Psychological requirement only | 1 | |
| Prophylactic supplement for breech extraction | 1 | |
| Supplement waning spinal effect | 1 | |
| Supplement the incomplete relief from spinal anesthesia (Effect wore off in 10 to 15 minutes) | 2 | |
| Between 1 hour and 1½ hours after the last injection | | 9 |
| Psychological requirement only | 4 | |
| Prophylactic supplement for breech extraction | 1 | |
| Supplement waning spinal effect | 2 | |
| Complete subsidence of the spinal anesthesia | 1 | |
| Incomplete relief following the 2nd injection | 1 | |
| Between 1½ hours and 2 hours after the last injection | | 4 |
| Psychological requirement only | 3 | |
| Supplement waning spinal effect | 1 | |
| Between 2 hours and 3 hours | | 14 |
| Psychological requirement only | 3 | |
| Prophylactic supplement for operative maneuvers | 5 | |
| Version and extraction on twin No. 2 | 1 | |
| Scanzoni maneuvers | 3 | |
| Breech (frank) extraction | 1 | |
| Supplement waning spinal effect | | 5 |
| Complete subsidence of spinal anesthesia | | 1 |
| Over 3 hours after the last injection | | 25 |
| Effective perineal anesthesia at delivery | | 13 |
| 3 to 4 hours after the last injection | 7 | |
| 4 to 5 hours after the last injection | 1 | |
| 5 to 6 hours after the last injection | 3 | |
| 7 hours and 22 min. after last injection | 1 | |
| 10 hours after the last injection | 1 | |
| Complete subsidence of spinal effect by delivery time | | 12 |
| Number of cases of complete failure (no relief at all) | | 3 |
| Total number of cases given anesthetics at the time of delivery | | 60 |

the patient to be carried through part of the first stage and all of the second and third stages with the minimum of discomfort. Because of the comfort, the patient is able to take adequate nourishment and fluids.

For the nursing staff, the care of the patient is made easy. Only the minimal equipment is required for the spinal injection in contrast to caudal anesthesia, and the nursing care is reduced to a minimum. Furthermore, the "last minute" confusion and excitement is eliminated as the time of delivery can be accurately predicted in the last hour.

From the physician's standpoint the advantages are many. Spinal anesthesia is the anesthetic of choice in cardiac patients, as well as in patients suffering from respiratory diseases, acute or chronic (e.g., tuberculosis, pneumoconiosis, bronchiectasis, asthma, upper respiratory tract infections, etc.). Furthermore, the danger of aspiration complications, often present in inhalation anesthetics, is eliminated. The use of low spinal anesthetics in patients given heavy pre-delivery sedation will save both the mother and the fetus, the additional narcotizing effect of the supplementary delivery anesthesia. Another advantage to the physician is the simplicity of administration.

The disadvantages of spinal anesthesia lie in the possible development of complications. The most important of these are the neurologic complications. Neurologic complications may follow general, as well as spinal anesthesia. Woltman¹⁰ found that convulsions, extrapyramidal rigidity, and postoperative psychosis followed general anesthesia almost exclusively. Courville¹¹ has shown that the anoxic hypoxia associated with weak anesthetic agents such as nitrous oxide and ethylene can cause degenerative changes in the cerebral cortex and lenticular nucleus. On the other hand, cauda equina syndrome, myelitis, neuritis, arachnoiditis, and septic and aseptic meningitis may follow spinal anesthesia. Scrupulous technique, using pure drugs in proper dilutions and vehicles, avoiding trauma at the time of injection, and selecting patients presenting no contraindications to the use of spinal anesthesia should reduce this danger to the minimum.

Drug reactions can be avoided by careful evaluation of histories followed by the skin or nostril test for sensitivity. The most common complication is the postspinal headache. This incidence can be reduced by withdrawing as little spinal fluid as possible at the time of puncture, by the early assumption of the sitting position, and early ambulation. Motor weakness during the anesthesia is transient and causes but slight inconvenience.

Summary

Three hundred seventy-five patients were given small doses of hyperbaric nupercaine solution to produce low spinal anesthesia. It provided satisfactory analgesia of at least one hour's duration in 370 patients. Perineal anesthesia, permitting episiotomy and episiorrhaphy, lasted on the average three to four hours, but in a few cases was found to be present as long as seven to ten hours. Recurrence of abdominal pain, however, appeared after two to three hours, and in some cases within two hours. Complementary and supplementary injections were generally more effective over a longer duration than the initial administra-

These two cases emphasize the need for routine testing for sensitivity.

Neurologic complications in spinal anesthesia as have been pointed out recently by Nicholson and Eversole⁹ are always potentially present. One case of foot drop is here presented.

No. 258.—A 29-year-old para iii was given 2.5 mg. of nupercaine 6 hours, 51 minutes, and again 1 hour and fifty-one minutes before delivery. Following initial injection, blood pressure fell to 34/14 mm. Hg, but responded promptly to ephedrine administration. No other unusual manifestation. Complete relief lasted only 45 minutes but partial relief for an additional hour. Complete relief with second injection and delivery and episiorrhaphy were uneventful.

She was allowed up on the third day but noted numbness of the right foot and calf, weakness of the right knee and ankle on walking. There was loss of dorsiflexion, inversion-eversion motions, and hyperesthesia was present over the dorsal-medial aspect of the right foot and ankle. Neurosurgical opinion was that the findings suggested localized injury to right L5 root.

To guard against neurologic complications, the following conditions should be met: (1) that the apparatus be scrupulously clean, (2) that the solution be free of deterioration and impurities, and (3) that no injection be made if the spinal puncture causes radiating pain or yields a bloody tap, as trauma to the nerve or cord may be produced as illustrated (these precautions, of course, are in addition to the contraindications previously listed).

Postspinal headache was another undesirable side-effect. Fifty-two patients developed headaches on the days indicated in Table IX. The headache was most frequently located in the upper cervical and suboccipital region, and to less extent over the frontal area. The headache was found to occur particularly on the day that the patient was permitted out of bed. That this headache may not be due to the anesthetic agent itself is indicated by the incidence of typical headaches following diagnostic spinal taps alone. Our incidence of postspinal headaches has dropped following the adoption of two precautionary measures: (1) minimizing the spinal fluid loss at the time of spinal puncture, and (2) early assumption of the near-upright position from the day of delivery.

Retained placenta occurred in one case, but as this patient had had retained placenta with her previous pregnancy, this cannot be truly classed as a complication of spinal anesthesia.

No. 344.—A 25-year-old para iv had had manual removal of retained placenta with her third delivery in 1944. She suffered much blood loss before the placenta was removed, and hence received 2 blood transfusions.

With this present delivery, 2.5 mg. of nupercaine were given 1 hour, 13 minutes before delivery. The placenta was retained and, because of persistent bleeding, manual removal was done. The placenta was adherent. Blood loss was about 500 cubic centimeters.

Comment

Spinal anesthesia presents advantages to the fetus, the laboring mother, the hospital staff, and the attending physician. For the fetus, spinal anesthesia provides maximum protection from two standpoints. Pharmacologically, the toxicologic drug reaction and depression to the baby are absent. Mechanically, the trauma to the baby's head is minimized by the elimination of the "bearing down" reflex; the cervix is dilated only by the action of the uterine contractions.

For the laboring mother, it provides absolute comfort. The patient is relieved of a great deal of pain almost immediately on injection of the hyperbaric solution. The prolonged analgesic and anesthetic effects of nupercaine allow

THE PSYCHIC COMPONENT OF PAIN IN GYNECOLOGY AND OBSTETRICS*

A Sensory Conditioning Process

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THE ever-crying need for more doctors, more nurses, and bigger and better hospitals will continue until all doctors come to realize that many of the afflictions of humanity are either disorders or distorted interpretations of sensory perception and not symptoms of structural or organic pathology.

Prevalence of Psychosomatic Factors

Cooke,¹ in his Chairman's address before the 1945 American Association of Obstetricians and Gynecologists and Abdominal Surgeons, stated, "The psychology factor is more important than the physical and functional pathology, . . . and 95 per cent of the severity of human suffering is mental." Bowman,² in an address before the 1946 General Scientific Assembly of the American Medical Association at San Francisco, estimated that 50 per cent of all cases seen in general medical clinics are primarily psychiatric problems, most of which would be labeled neuroses. Parran³ reported in February, 1947, that there are 8,000,000 psychically ailing Americans in urgent need of care. Read,⁴ in his book *Childbirth Without Fear*, is convinced that the most of the discomforts of pregnancy and pain of childbirth are products of our culture.

Heyns⁵ calls attention to the absence of psychosomatic complaints in primitive woman. In his article, "The Superiority of the South African Negro as a Parturient," he makes this statement: "There is present a fortitude and an acceptance of the situation such as is rarely seen in the European, and hardly ever seen in the latter when cases of dystocia alone are considered." Aaberg,⁶ who has just returned from Guam, reports that nausea and vomiting is rarely, if ever, present in the primitive woman; that the pain of childbirth is of no importance until the native comes in contact with culture.

Bennett,⁷ in a paper on "Faulty Management of Psychiatric Syndromes Simulating Organic Disease," investigated the case histories of 150 neurotic patients and found they had been subjected to 496 medical treatments, 244 surgical treatments, and 71 admitted cultist treatments; a total of 811 therapies prior to any psychiatric attention. Alvarez, Mackay, and Menninger, in a discussion of Bennett's paper, blame such mismanagement upon faulty medical education, laziness, lack of imagination, and a worship of technical and chemical procedures on the part of the physician.

There are, however, a certain number of diligent doctors who, because they meet with a certain amount of success by the use of their particular therapy, find it expedient to continue the use of therapies which for the most part are approved medical and surgical placebos. There are also some sincere physicians who through biased medical training interpret pathology where no actual pathology exists.⁹ They are continually finding what they are looking for and

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tion. Hypotension requiring the use of ephedrine occurred in 13 patients and of the 13, two developed "reactions" (hypotension, bradycardia pallor, cold sweats, and fetal heart irregularity) which responded satisfactorily to the administration of oxygen and ephedrine. In all of the 375 patients some motor weakness was present. The area of anesthesia and hypesthesia described a saddle pattern over the legs and perineum and extended over the abdomen to various segmental levels, for the most part below the level of XI thoracic nerve. Blood loss at the time of delivery was usually small but, as the minimal dose of nupercaine was not always used, no conclusions can be drawn. In all cases except six the babies were awake, breathed, and cried as soon as the heads were delivered. There were three stillbirths. In two cases, the patient gave birth to twins, in each of which one twin was a macerated stillborn infant. In both of these cases the labors were premature. Fifty-two patients developed headaches on various days of the puerperium. A neurologic complication, in the form of foot drop, occurred once.

Conclusion

Low spinal anesthesia and analgesia for parturition is definitely satisfactory to the patient and her relatives, to the nursing staff, and to the obstetrician because of the dramatic and effective relief of the discomfort of labor, the maximum safety it provides the fetus and the mother, and the simplicity of the technique which utilizes a minimum of paraphernalia. That there are certain dangers to its use must be borne in mind at all times. Protracted or permanent neurologic complications may follow spinal anesthesia as well as general anesthesia. Drug reactions may endanger the fetus and the mother. It is, therefore, imperative that the most careful technique be closely observed.

Since the advantages are many and the disadvantages few, it is our belief that low spinal anesthesia is the anesthesia of choice in obstetrics.

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should be remembered that cortical cells have the function of spontaneous activity, and that pain can appear spontaneously through association with some previous painful experience. For instance, the hypnotist through suggestion is able to reinstate the vivid pain of toothache only if his subject has once experienced such toothache.

Using college students as subjects, laboratory investigators have found that the constant repetition of painful electrical stimuli to the skin would continue to produce the sensation of pain in the skin after about the 200th application, even though the stimulus was only feigned. In other words, once a subject's pain perception becomes associated with the mechanical apparatus, the sight and click of the mechanism alone are sufficient to produce the sensation previously initiated.

As with all cells a threshold stimulus is necessary for excitation. Hardy, Wolff, and Goodell,¹¹ and others have found the pain threshold rather constant in the unprejudiced subject. If this were not the case subliminal impulses would reach consciousness and we would be continuously annoyed by the normal activities of the body.

If the above phenomenon were constant all individuals would perceive pain alike, and the reactions to pain would be in direct proportion to the stimuli applied. Unfortunately, or fortunately, as the case may be, the perception of pain is affected by the attitude of the patient, so that in combat or in games in intense excitement the participants are often unaware of severe injury, the apprehensive individual may suffer pain even before being touched.

Haman¹² has found that the pain threshold is slightly lower in dysmenorrhoics and others who appear preternaturally sensitive.

The disparity, however slight, is often sufficient to cause one individual to feel impulses of pain to which another would remain indifferent. Once impulses are recognized as painful they become associated or integrated with previous and coincidental environment. Repetition tends to strengthen these connections so that mosaic patterns of excitation or inhibition are created in the cerebral cortex—patterns which profoundly alter the bodily reactions. This process of learning to feel pain is analogous to the same sensory conditioning process inherent in other learning and reasoning—like learning to speak or to appreciate music.

Some persons so strongly identify events, objects, smells, taste, or noises with painful experiences that every time they subsequently encounter a like event, object, or sensation, a painful reaction is felt. Thus the screech of a siren may cause pain and collapse in an individual who has recently experienced an automobile accident. This is known as *synthesia*. With this explanation we arrive at approximately the same conclusion as Read. A stimulus of a fixed magnitude applied to any specific sensory receptor produces a psychic sensation and a somatic reaction commensurate with the intensity of its interpretation.

It is normal, of course, for the human being to seek the cause for the painful impulses that register in his consciousness. It is only when he has exaggerated the pain by anticipation, concentration, or anxiety, to an intolerable point that his neurosis becomes abnormally troublesome to him and makes of him a misfit

ignoring anything that is contrary to their expectations, their opinions or their convictions. This is often true of various specialists and invariably true of most cult healers.

It is not difficult for the gynecologist and obstetrician to detect the fully developed psychoneurotic patient after a few minutes' conversation, but to detect the prodromal symptoms or the incipient stage takes time and patience. As a matter of fact, there is no such thing as an exact line between functional and organic symptoms. It is merely a matter of degree. All organic ailments have functional modifications, and functional disorders can produce organic changes.

Development of Neuroses

The masses, through shorter working hours, possess the gift of leisure without much preparation for the enjoyment of it. The human being, by nature introspective, quickly focuses his spare attention upon that most precious of his possessions—his body. He discovers vague pains which begin to harass him. The more profound his concentration, the more severe becomes his agony. Listening to the radio or reading the paper tends to exaggerate his preoccupation with the cenesthetic functioning of his body. Every hour of the day he is startled into searching for new symptoms. The public easily manifests the symptomatology it hears discussed; agrees with the popular plaint regarding the need for more doctors, nurses, and hospitals; feels the whole population is entitled to the most lavish medical care. The fact that the severity of his pain may be psychic in origin is either unintelligible to the average man or simply incredible. To the sufferer his pain is very real. He wants relief.

Psychobiology of Pain

It is astonishing how little use is made of pain in establishing a diagnosis, or directing the management of a disorder. We have passed through a period in which pain was always considered a symptom secondary to tissue pathology, and are now beginning to regard it in its true sense as a sensory perception. Until the medical profession as a body becomes habituated to the idea that there is an important *difference* between the patient's perception of pain and his reaction to painful experience with its autonomic, emotional, and other components, confusion is bound to persist. Once this difference is accepted, the reactions to pain such as sweating, tachycardia, dyspnea, anorexia, intestinal disturbances, *as well as* anxiety, fear, panic, fatigue, and prostration can be evaluated and better managed.

Lewis,¹⁰ who has spent a lifetime in the study of pain, says, "Pain cannot be defined; it is something we learn from experience and describe by illustration."

The function of the sensory nervous system is to acquaint the conscious mind with the nature of the external and internal environment—light, odor, taste, sound, pain, temperature, and pressure—in order to regulate autonomic processes and coordinate muscular movement. The newborn infant is unaware of the first noxious stimulus, but by repetition and spatial summation preception occurs, and in time is projected to the definite area of irritation. Also, it

patient—and often his doctor—thinks it is. Wolff¹³ states that nervous stimulation is a centrally integrated experience projected onto the periphery for specific purpose of localization. The “skin spot” is a “mind spot.” In most amputation cases pain disappears with the proper healing of the stump. Yet surgeons everywhere and many among the laity are acquainted with amputees who complain for many months, sometimes throughout the remainder of life, of pain felt in the removed member. Neurectomy, rhizotomy, decortication of vessels, cordotomy, and intraspinal alcoholic injections are frequently employed, without relief, on the same patient. Such a patient may become addicted to alcohol, barbiturates, opiates, or he may even choose suicide in a desperate attempt to gain release from pain.

Any amputee will admit that he remains most acutely conscious of that part of his missing member upon which his attention was fixed often just previous to amputation. Livingston's¹⁴ railroad employee, who was attempting to remove gravel from the fingertips of his glove when struck by a train continued to feel the aggravation of the gravel at his missing fingertips more than the pain of amputation which had been performed at the shoulder.

Another amputee had undergone 13 surgical operations on the stump for the relief of phantom limb pain before van Wagenon of the Mayo Clinic severed the nerve connections between the cortex and the basal ganglion (lobotomy) and relieved the patient. This not only illustrated the inflexibility of some orthopedic surgeons, but should prove that *pain* is a perception—and as such becomes a function of the cerebral cortex. The fingers and toes, where there is the greatest concentration of sensory nerve terminals, naturally have the greatest representation in the cortex and so are most frequently the parts that give postamputation trouble.

Persistent pain in other parts of the body responds to lobotomy in the same way as phantom limb pain. Where pain patterns have become fixed by a long-continued sensory conditioning process, severance of the cortico-thalamic tracts often results in relief—even of such intractable pain as that of inoperable pelvic carcinoma.¹⁵ Freeman and Watts state that many patients report they still feel pain but in a different manner. The emotional factor is gone and along with it the persistent demand for narcotics.

Disorders of Perception

The psychic factors in gynecologic and obstetric disorders develop for the most part through exaggeration of normal physiologic impulses. By suggestion, persuasion, introspection, and fear some patients perceive subliminal impulses of which normally they would be unaware. Many individuals, unfortunately, are born with a lowered pain threshold and throughout their lives are considered by their friends hypersensitive, delicate, and neurotic.

Evaluation of Statistics

The mistakes that doctors make in the evaluation of statistics, which lead to the misdiagnosis and mismanagement of functionally ill persons, is the result

in the social pattern. Proof of the psychic origin of many neuroses lies in the spectacular improvement of many patients—where the treatment administered is totally unrelated to either the complaint or to the diagnosis.

Illustrative Cases

CASE 1.—A dramatic example is a recent case of a missed abortion. Some time elapsed before a positive diagnosis was made. The patient's husband became apprehensive of her developing "blood poisoning." Evacuation of the uterus was accomplished with difficulty. For a month the patient complained of a putrid discharge, then delivered a fetal appendage. She became greatly alarmed, lost confidence in her physician, and began to develop pelvic pain and numbness in the left side of her body. Although no pathology could be found, she became worse. A consultant halfheartedly advised an exploratory laparotomy. The patient's alarm increased and her numbness changed to partial paralysis, which spread to the right arm. Also her abdominal pain increased. Her husband took the patient to another physician who deliberately convinced her that her pain and disability were caused by vascular constriction in the affected parts. She was assured release could be accomplished by three specific intravenous injections (glucocalcium). Urging the patient to watch for immediate flushing and a feeling of warmth over her entire body, to focus her whole attention upon her physical reaction to the injections, released her anxiety and produced the bodily response expected. Diagnosis; hysteria. Treatment: Reassurance with the aid of a placebo. Result: Immediate improvement, with complete relief within a week.

CASE 2.—This case is cited to demonstrate that full recovery of patients from troublesome symptoms may follow surgery where *no* pathology was found. A pregnant patient complained of pain in the right lower quadrant—a common enough symptom. At her prenatal visits her fears were temporarily allayed by rationalization and reassurance that it was believed the birth of her child would put an end to her symptoms. Subsequent to delivery, her symptoms recurred and continued to do so every three or four months. Her physician continued to use suggestion and persuasion to restore her confidence, but always with only temporary relief. At the end of a year the patient's husband telephoned to say he was firmly convinced his wife was suffering from chronic appendicitis. Without again seeing the patient her physician referred her to a surgeon who booked her for operation, requesting his assistance. In the dressing room the obstetrician asked the operating surgeon as a favor to impress the patient with the *severity* of her lesion—regardless of what he should find—and to convince her he had removed the trouble. Treatment: Removal of a normal appendix. Result: Immediate and permanent cessation of symptoms.

Conversely, definite pathology may be found and removed and the patient insist that her trouble and her pain continue.

CASE 3.—Mrs. J. W. had an offensive, persistent rectovaginal fistula. Over a period of years several unsuccessful attempts were made to close the opening. Finally the fistula was successfully closed. Nevertheless, the patient continued to feel unclean and insisted that intestinal gas and secretions still pass to the vagina. The most careful examinations by various doctors only temporarily convinced her that the fistula was closed.

Phantom Limb Pain

Perhaps a consideration of the pain of phantom limb will illustrate more effectively than any gynecologic case history that pain is not always where the

Few patients can be convinced that actually nothing is pathologically wrong with the functioning of their bodies. To them their suffering is real, and not imaginary as too many suppose.

In the treatment of a disagreeable neurosis, the sufferer must be provided with some avenue of escape. The patient must approve the diagnosis given and be convinced that the cause of the trouble can and will be removed. If this were not true, all "medical cults" would perish. In many cases the surgeon removes the cause by some operation; the internist by giving a pill or an injection; the psychiatrist by bringing to life some real or alleged childhood repression; the psychologist by hypnosis, producing disregard of pernicious stimuli or substitution of an agreeable association.

In all therapies, the attitude of the patient is a most important factor. This is particularly true in either ameliorating or intensifying the discomforts of pregnancy and the pain of parturition. It is equally true of pelvic pain, particularly essential dysmenorrhea.

It is apparent that this primitive protective physiological sensation becomes perverted to the disadvantage of the individual and the nation. It is important that the practicing physician recognize pain as a perception and not judge it solely by the reactions.

Summary

1. An attempt has been made to show that the ever-increasing afflictions of humanity are for the most part disorders of sensory perception and not symptoms of structural pathology.

2. The perception of pain is a psychobiological product of evolution and its intensity is the result of a sensory conditioning process.

3. Illustrative cases of psychosomatic disorders are presented.

4. Medicine of the future must be more educational than curative and attack environmental causes of disorders rather than structural changes of disease if it hopes to overtake the rate of increase of ailments.

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of biased thinking. Specialists in general are often so prejudiced by their own particular methods of therapy they frequently neglect to realize that not only do these methods fail of the desired effect . . . but indeed of any effect whatsoever. It is for this reason that the treatment for any psychosomatic ailment varies from decade to decade, but the percentage of relief obtained remains approximately the same. For instance, school children are subjected to removal of tonsils, yet the widespread practice of this operation has failed to lower the incidence of colds, arthritis, or heart disease. Dorcus,¹⁶ in appraising the statistical results of approved medical procedures as applied to mental patients for the past one hundred years, has found that the percentage of relief has not improved.

Discussion and Conclusion

Most of the diseases that fifty years ago required the greater part of the physicians' time have been eradicated through improved hygiene and sanitation; through immunization, antibiotics, and chemotherapy. In addition to this, medical efficiency has increased and medical facilities have been expanded. Yet, instead of a decrease in the numbers of the ailing, the multitudes clamoring for relief has multiplied constantly. The reason is obvious. In every country, in every age, where man is released from privation and the pursuit of the necessities of life, he becomes aware of the person in the body. But this is not enough; he has turned his attention upon himself. By nature introspective, he begins to search his internal as well as his external environment for new and different sensations. In this search he discovers some of the normal activities of his body. His awareness of these functions does not necessarily carry with it full understanding of them and he frequently misinterprets them as abnormalities.

It is almost inevitable that he associates his internal findings with some of the facts, feelings, and ideas collected from his external world. Acceptable and unacceptable impressions are integrated with various specific sensory impulses, giving rise to agreeable and disagreeable sensations and reactions to them. He is likely to misinterpret such reactions as symptoms of disease. In reality they are disorders of perception or distorted interpretations of sense perceptions. They create in the individual fear and nervous tension. Naturally he fixes his attention on some innocent organ to express his abstract feelings and the organ "speaks."

Neuroses can be produced experimentally in animals where the avenue of escape from noxious stimuli is blocked. In primitive peoples they are induced by the incantations of witch doctors; in the more civilized peoples they are produced by suggestion and introspection. Neuroses are, therefore, the result of sensory conditioning processes and usually can take one of three courses:

1. The impressions may be disregarded and, so, have apparently no effect.
2. The impressions may be associated with agreeable sensation and prove beneficial.
3. The impressions may become associated with disagreeable sensations and lead to discomforts.

TABLE I

| CASE | AGE | ONSET OF MENSES | AMENOR- RHEA | BASAL METABO- LISM RATE | URINARY HORMONE ASSAY | GLUCOSE TOLERANCE | VAGINAL pH | VAGINAL SMEAR |
|------|-----|--------------------|-----------------|----------------------------------|---------------------------------|----------------------|---------------|-------------------------|
| 1 | 21 | None | Primary | +4 | Negative FSH Negative Estrin | Flat curve | 5-8 | Sub estrone |
| 2 | 21 | None | Primary | -3 | Positive FSH Traces Estrin | Normal | 5-8 | Sub estrone |
| 3 | 19 | None | Primary | -10 | Positive FSH Negative Estrin | Normal | 5-7 | Sub estrone |
| 4 | 20 | None | Primary | -7 | Negative FSH Negative Estrin | Flat curve | 5-8 | Castrate-sub estrone |
| 5 | 21 | None | Primary | -4 | Negative FSH Traces Estrin | Normal | 5-8 | Sub estrone |
| 6 | 20 | None | Primary | +1 | Positive FSH Traces Estrin | Normal | 5-8 | Sub estrone |
| 7 | 18 | None | Primary | +3 | Negative FSH Traces Estrin | Flat curve | 5-8 | Sub estrone |
| 8 | 19 | None | Primary | -5 | Positive FSH Negative Estrin | Normal | 4-7 | Sub estrone |
| 9 | 18 | None | Primary | +9 | Negative FSH Negative Estrin | Flat curve | 5-8 | Castrate-sub estrone |

5. Vaginal smears became fully cornified in all patients in this group after taking ethinyl estradiol.

6. The pH studies did not run parallel to the vaginal smears and were of no value as an indication of estrogenization.

7. Eight patients, or 14 per cent, had nausea and vomiting, but in no instance was this severe enough to necessitate stopping of medication.

8. Vaginal bleeding was noted in nine patients, or 20 per cent, but was never severe. Bleeding always stopped with cessation of therapy. In a number

TABLE II. SECONDARY

| CASE | AGE | ONSET OF MENSES | AMENOR- RHEA (MONTHS) | BASAL METAB- OLISM RATE | URINARY HORMONE ASSAY | GLUCOSE TOLERANCE | VAGINAL pH | VAGINAL SMEAR |
|------|-----|-----------------------|-----------------------------|----------------------------------|---------------------------------|----------------------|---------------|-------------------------|
| 1 | 19 | 16 | 4 | - 6 | Negative FSH 3 RU estrin | Normal | 4-6 | Sub estrone |
| 2 | 24 | 16½ | 6 | - 4 | Negative FSH Traces estrin | Flat curve | 4-5 | Sub estrone |
| 3 | 22 | 14 | 4 | -11 | Negative FSH Traces estrin | Flat curve | 4-7 | Sub estrone |
| 4 | 35 | 14 | 4 | + 5 | Negative FSH Negative estrin | Flat curve | 4-8 | Castrate-sub estrone |
| 5 | 21 | 14 | 4 | + 2 | Negative FSH Traces estrin | Normal | 5-8 | Sub estrone |
| 6 | 26 | 15 | 5 | - 7 | Positive FSH Negative estrin | Normal | 4-5 | Sub estrone |
| 7 | 22 | 15 | 4 | - 1 | Negative FSH 3 RU estrin | Normal | 5-6 | Sub estrone |
| 8 | 20 | 14 | 4½ | + 6 | Negative FSH Traces estrin | Normal | 5-6 | Sub estrone |
| 9 | 20 | 15 | 5 | - 1 | Negative FSH Negative estrin | Flat curve | 5-8 | Castrate-sub estrone |
| 10 | 19 | 15½ | 4 | 0 | Negative FSH 5 RU estrin | Normal | 5-8 | Sub estrone |

ETHINYL ESTRADIOL

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THE advantages of a potent oral estrogen are obvious. The need for such a preparation has, in recent years, prompted the appearance of numerous estrogens for oral use. Several such preparations were tested in a group of animal experiments. The material was fed to castrated female rats of standard size. The extent and duration of the estrogen effect was noted by means of daily vaginal smears. These studies will be reported in detail at a later date. However, of this group, ethinyl estradiol proved the most potent, and observations on its clinical use are the subject of this paper.

Ethinyl estradiol is a derivative of the natural follicular hormone alpha-estradiol, in which an ethinyl group replaces the hydrogen atom attached to the carbon atom in position 17 of the estradiol nucleus. Peculiarly, the introduction of the ethinyl group which has an acetylene linkage, ordinarily associated with chemical instability, brings to the molecule properties which markedly increase the efficacy when orally administered.

Ethinyl estradiol was used and its effects observed in the following conditions:

1. The menopause.
2. Amenorrhea, primary and secondary.
3. Suppression of postpartum lactation.
4. Labor.

Menopause.—Fifty-seven menopausal women were treated with ethinyl estradiol. This group included patients suffering from both surgical and natural menopause. A number of these patients had previously received other estrogenic preparations.

In all patients hormone assays were done, consisting of urine F.S.H. levels and urine estrone excretion, prior to the starting of therapy. In every instance in this group, F.S.H. was present and estrone was absent in the urine, prior to the starting of therapy. Vaginal smears and pH studies of vaginal secretions were done before, during, and after therapy.

The dose was one, two, or three tablets of 0.05 mg. of ethinyl estradiol daily, depending on the severity of the symptoms. After the symptoms were controlled, the dose was gradually reduced, and in many cases one tablet every seven to ten days was sufficient as a maintenance dose.

The following is a summary of our results in this group:

1. Forty-five patients, or 79 per cent, had complete relief from menopausal symptoms such as flushes, sweats, insomnia, nervousness, etc.
2. Ten patients, or 17 per cent, had moderate relief.
3. Two patients, or 4 per cent, had no relief.
4. All patients who obtained relief experienced a general feeling of well-being.

TABLE III. SECONDARY

| CASE | AGE | ONSET OF MENSES | AMENOR- RHEA (MONTHS) | BASAL METAB- OLISM RATE | URINARY HORMONE ASSAY | GLUCOSE TOLERANCE | VAGINAL pH | VAGINAL SMEAR |
|------|-----|-----------------------|-----------------------------|----------------------------------|---------------------------------|----------------------|---------------|-------------------------|
| 1 | 18 | 15 | 5 | -5 | Positive FSH Traces estrin | Normal | 4-6 | Sub estrone |
| 2 | 18 | 16 | 4 | +3 | Negative FSH Negative estrin | Flat curve | 5-8 | Sub estrone |
| 3 | 22 | 16 | 8 | +1 | Positive FSH Negative estrin | Normal | 6-8 | Castrate-sub estrone |
| 4 | 21 | 16½ | 6 | -7 | Negative FSH Negative estrin | Flat curve | 4-6 | Sub estrone |
| 5 | 21 | 15 | 5 | -4 | Negative FSH Traces estrin | Flat curve | 4-6 | Sub estrone |

manifested by a diminution in the size of the uterus and cervix, and, although the cause of the amenorrhea may be subsequently corrected, regular menstruation will not occur if the uterus and cervix remain hypoplastic. Our procedure with these patients, therefore, is to determine the cause of the amenorrhea, by means of a thorough investigation of the patient's endocrine status. The therapy is then directed at stimulating the growth of the uterus and cervix. This is accomplished by the administration of estrogens in sufficient dosage. By interrupting therapy at regular intervals, bleeding occurs. This is estrogen withdrawal bleeding and is psychologically highly desirable and encouraging to the patient. With this type of intermittent therapy, not only is the pituitary function not depressed, but in all probability it is stimulated.

The patient was considered amenorrheic if she had not bled for a period of at least four months. There were twenty-four patients in this group. Nine of these patients had primary amenorrhea—in this group menarche had not occurred. Their ages ranged from 16 to 21 years, and all were unmarried. Fifteen patients had secondary amenorrhea—these patients had previously menstruated. Their ages ranged from 16 to 35 years. Ten of this group were married, and five were single.

Ethinyl-estradiol—0.05 milligrams—was given daily for twenty days, followed by a 10-day interval during which medication was discontinued. In most instances bleeding occurred during this interval. The size of the uterus was noted periodically, and this therapy was continued until the uterus was normal in size. This took from three to six months, depending on the duration of amenorrhea and the degree of uterine hypoplasia. In resistant cases, the daily dose was doubled in order to produce uterine growth and bleeding.

Endometrial biopsies were done on all married patients¹⁰ with secondary amenorrhea, before, during, and after treatment.

The results are noted below:

1. All patients were made to bleed periodically.
2. Growth of the uterus and cervix was accomplished in all cases. The patients with primary amenorrhea required more prolonged treatment and larger doses to produce uterine growth and bleeding.
3. In those patients where endometrial biopsies were done, bleeding was noted from a proliferative endometrium during the therapy. Six patients, on whom follow-up biopsies were done seven to twelve months after the cessation of therapy, showed secretory endometrium four months after treatment was stopped. Two patients, although they were bleeding regularly, failed to show any secretory endometrium as late as two years after therapy was stopped.

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MARY AMENORRHEA

| SIZE OF UTERUS | | DURATION OF TREATMENT | ENDOMETRIAL BIOPSY | SIDE EFFECTS | RESULTS |
|---------------------------|--------------------------|-----------------------|--------------------------|-----------------|---|
| BEFORE TREATMENT (INCHES) | AFTER TREATMENT (INCHES) | | | | |
| 1½ | 3 | 1 year | Not done | Painful breasts | Good |
| 1½ | 3½ | 14 months | Secretory after marriage | None | Good |
| 1 | 3 | 16 months | Not done | None | Baby 15 months after marriage |
| 1 | 3½ | 19 months | Not done | None | Good |
| 2 | 3½ | 9 months | Not done | None | Good |
| 1½ | 3 | 10 months | Not done | None | Good |
| 1½ | 3½ | 10 months | Secretory after marriage | None | Good |
| 1½ | 3½ | 8 months | Not done | Painful breasts | Good. Baby 11 months after marriage. Pregnant again |
| 1 | 3 | 8 months | Not done | None | Good Good |

of patients it was then possible to resume ethinyl-estradiol therapy with somewhat reduced doses, without a recurrence of bleeding.

9. Six patients with extremely severe symptoms responded more rapidly if parenteral estrogen therapy was first instituted in the form of alpha-estradiol-benzoate—1.3 mg. given twice weekly intramuscularly. These patients were given oral ethinyl-estradiol after some improvement was noted on this regime and improvement continued.

Amenorrhea.—It is our concept that in amenorrhea of sufficient duration, regardless of the etiologic factor, there are marked involutionary changes,

AMENORRHEA (MARRIED)

| SIZE OF UTERUS | | DURATION OF TREATMENT (MONTHS) | ENDOMETRIAL BIOPSY | SIDE EFFECTS | RESULTS |
|---------------------------|--------------------------|--------------------------------|---|-----------------|---------|
| BEFORE TREATMENT (INCHES) | AFTER TREATMENT (INCHES) | | | | |
| 2 | 3½ | 4 | Proliferation, secretory, 8 months later | Painful breasts | Fair |
| 2 | 3½ | 4 | Proliferation, secretory, 12 months later | Painful breasts | Fair |
| 2 | 3½ | 3 | Proliferation | None | Good |
| 1½ | 3 | 6 | Proliferation | Nausea | Good |
| 2 | 3½ | 4 | Proliferation, secretory, 10 months later | Painful breasts | Good |
| 1½ | 3½ | 4 | Proliferation | None | Good |
| 2 | 3 | 5 | Proliferation, secretory, 7 months later | None | Good |
| 2 | 4 | 3 | Proliferation, secretory, 11 months later | Painful breasts | Good |
| 2 | 3½ | 5 | Proliferation, secretory, 8 months later | None | Good |
| 2 | 4 | 7 | Proliferation | None | Good |

Five of the total number of patients in this group reported vaginal staining during the first three weeks following their discharge from the hospital.

It is apparent then that three out of four patients can expect to have satisfactory results in suppression of lactation and engorgement by using ethinyl estradiol in the manner described.

2. Nursing mothers.

The same dosage schedule was used in twenty-six nursing mothers with the following results:

There was no suppression of lactation or breast engorgement in six patients.

There was partial suppression of lactation and breast engorgement in seventeen patients.

Complete suppression of lactation and breast engorgement was obtained in spite of regular nursing of infants in six patients.

Labor.—Ethinyl-estradiol was used to influence labor in forty-nine patients. This group was divided into patients in whom it was desired to induce labor (fifteen patients), and patients who were experiencing a slow nonprogressive type of labor (thirty-four patients).

The dose used was 6 tablets 0.05 mg. ethinyl estradiol every two hours up to 15 doses. There were no side effects as the result of this treatment.

The results were as follows:

1. In the group of 15 patients in which ethinyl estradiol was used to induce labor, the treatment was successful in ten cases, and without effect in five. In the ten successful cases, five patients were delivered within twelve hours after the start of the treatment; two patients were delivered twenty-six hours after the therapy was started; two were delivered in twenty-six hours; and one was delivered in thirty hours.

2. In the group of thirty-four patients in which this regime was used to hasten labor, the therapy was apparently successful in thirty cases and without results in four patients. In the successful group, twenty-six patients delivered within twelve hours, and four delivered within twenty hours.

Summary

1. Ethinyl-estradiol is an extremely potent oral estrogen.

2. Moderate or complete relief from menopausal symptoms was obtained in 96 per cent of patients. Toxic symptoms were negligible.

3. Growth and development of the hypoplastic uterus as well as bleeding was accomplished in 100 per cent of patients with primary and secondary amenorrhea.

4. Inhibition of lactation was effected in 75 per cent of nonnursing mothers without untoward results, and there was no excessive postpartum bleeding.

5. The use of ethinyl estradiol in the induction and hastening of labor is presented.

We are indebted to Dr. Erwin Schwenk and Dr. Edward Henderson of the Schering Corporation for their cooperation and generous supply of material.

AMENORRHEA (UNMARRIED)

| SIZE OF UTERUS | | DURATION OF TREAT- MENT (MONTHS) | ENDOMETRIAL BIOPSY | SIDE EFFECTS | RESULTS |
|--------------------------------------|-------------------------------------|---|-----------------------|----------------------------------|---------|
| BEFORE TREAT- MENT (INCHES) | AFTER TREAT- MENT (MONTHS) | | | | |
| 2 | 3½ | 6 | Not done | Painful breasts | Fair |
| 2 | 3½ | 5 | Not done | Painful breasts | Good |
| 1½ | 3½ | 5 | Not done | Vaginal bleeding and spotting | Good |
| 1½ | 3 | 4 | Not done | Nausea | Good |
| 2 | 3½ | 4 | Not done | Vaginal bleeding and spotting | Good |

4. In those patients with primary amenorrhea and poor breast development, there was considerable development of the breasts and increase in the size of the nipples noted after the treatment. Eight patients complained of painful breasts which subsided after treatment was discontinued.

5. Two patients complained of mild nausea of a degree which did not necessitate cessation of therapy.

6. Two patients of the primary amenorrhea group were subsequently married, and have had one child each.

Tables I, II, and III give a detailed summary of the endocrine status, response to therapy, and biopsy follow-ups of the patients in this group.

Inhibition of Postpartum Lactation.—Ethinyl-estradiol was used to prevent breast engorgement and inhibit lactation in 145 nonnursing postpartum mothers. The effect of ethinyl estradiol on the lactating breast was studied in 26 nursing postpartum mothers.

1. Nonnursing mothers.

Thirty tablets of ethinyl estradiol, 0.05 mg., were given to the patients in this group over a period of nine days, starting within twenty-four hours of the time of delivery. The dose was administered as follows:

First three days—2 tablets three times daily.

Following three days—1 tablet three times daily.

Last three days—1 tablet daily.

Patients were observed during their stay in the hospital and were followed for a period of three to four weeks at home.

The absence of lactation and engorgement for a period of one month following delivery was classified as an excellent response. The result was noted as good, if slight engorgement or slight leaking without engorgement occurred for a day or two during the course of the therapy or after the patient left the hospital. It was considered fair if engorgement was more than slight or lasted more than two days and was associated with some leaking. The result was regarded as poor if there was moderate or full breast engorgement associated with leaking, and lasting several days.

No other form of medication was given, and breast support was not used except in those patients classified as poor.

The results are summarized as follows:

| | |
|-----------|---------------------------|
| Excellent | 85 patients (58 per cent) |
| Good | 23 patients (16 per cent) |
| Fair | 22 patients (16 per cent) |
| Poor | 15 patients (10 per cent) |

mones. Very little or no glycogen is being formed or stored in the epithelial cells of the endometrium during this phase which is largely one of growth.

Fifteen patients having evidence of acute gonorrhea were examined during this phase. The pH range of their cervical mucus was 7.6 to 6.8. Eleven had positive cultures and four had negative cultures.

2. Ovulation, twelfth through sixteenth day. This division of days is based upon the findings of Allen, Pratt and Newell,⁴ who washed out tubes exposed at operation and were not able to recover ova prior to the twelfth day or later than the sixteenth day. During this time estrogenic activity is at its peak and the columnar cells of the cervical glands yield their greatest amount of mucus.

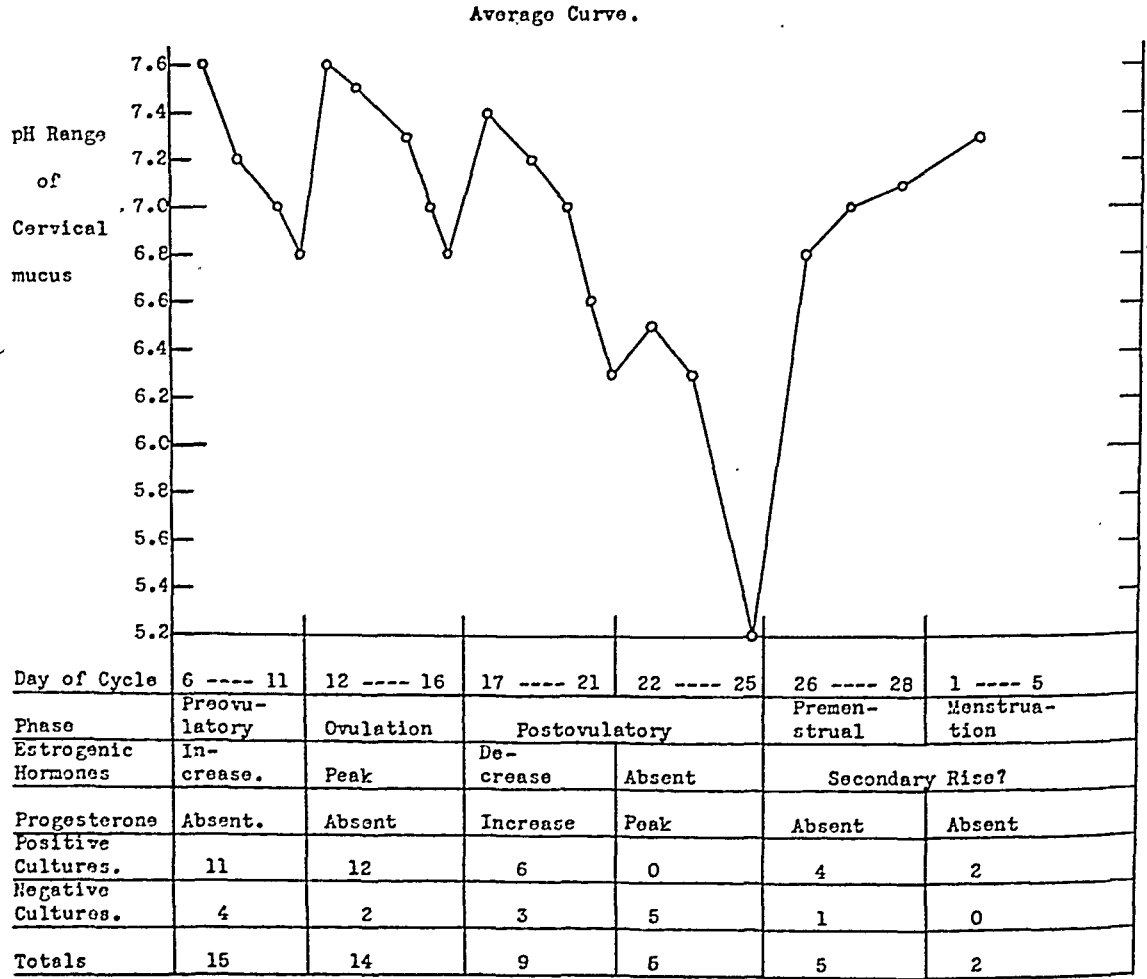


Fig. 1.—Results of cervical cultures on fifty dispensary patients suspected of having acute gonorrhea, with regard to the pH of the cervical mucus and phase of the menstrual cycle.

Fourteen patients suspected of having acute gonorrhea and whose pH range was 7.6-6.8 were examined. Twelve had positive cultures, and two had negative cultures.

3. Postovulatory or secretory phase, seventeenth through twenty-fifth day. There is a gradual decrease in estrogens, and the endometrium and cervical glands come under the influence of progesterone. During this time glycogen is being formed in the cells of the endometrium and is also being rapidly excreted. Pommerenke⁵ demonstrated that the largest amount of fermentable carbohydrate in the cervical glands occurs at this time.

A STUDY OF CERVICAL CULTURES TAKEN IN CASES OF ACUTE GONORRHEA WITH SPECIAL REFERENCE TO THE PHASES OF THE MENSTRUAL CYCLE

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THE question of why so many negative cultures have been obtained from patients having clinical pictures of acute gonorrhea has long been a puzzling one to bacteriologists. The favorite explanation has been the lack of a sufficiently nutritive medium upon which to grow the organism. The use of pancreatic digest agar containing 5 to 10 per cent human chocolate blood, as described by Koch,¹ should have overcome the cultural difficulties; nevertheless an undesirable number of negative cultures are still being obtained.

In 1940, Lamar, Shettles, and Delfs² showed that there was a relative change in the alkalinity and acidity of the cervical mucus during the menstrual cycle, and that there was a positive correlation with the penetrability of spermatozoa between these changes and other factors.

It seemed possible that the cyclic changes in the cervical mucus might also have an effect upon the viability of the gonococcus in vivo.

Material

As a preliminary investigation, 50 histories of patients whose cervixes were cultured because of suspected gonorrheal infection were studied with regard to the menstrual cycles. The date of culturing the cervical secretion was noted in relation to the date of the menstrual cycle. The results showed that in the first half of the cycle when the pH of the cervical mucus is greater than 6.8, 66.0 per cent of the cultures were positive, and in the last half of the cycle when the pH is less than 6.6, only 10 per cent were positive.

Since this preliminary study suggested that there might be a correlation between the cervical mucus pH and the ability to culture the gonococcus, further studies were immediately undertaken.

The cervixes of 50 patients suspected of having acute gonorrhea and having normal menstrual cycles were cultured and smeared, and the cervical mucus pH determined. The method used was as follows: mucus was aspirated from the cervical canal by means of a sterile, curved, capillary glass pipette fitted with a rubber bulb. The pH of the sample was immediately tested by using a series of buffer solutions and indicators as described by Brown.³

Results

The normal menstrual cycle, consisting of approximately twenty-eight days, was divided into phases based upon the action of the two ovarian hormones (Fig. 1).

1. Preovulatory or proliferative phase, sixth through eleventh day. At this time the cellular changes are under the influence of the estrogenic hor-

Of the 35 positive cultures, 30 were isolated in pure culture and all fermented dextrose only.

These results led to further investigations to determine whether patients having positive cultures during the estrogenic phases of their cycles, and negative cultures during the phase of progesterone activity, would again yield positive cultures during the estrogenic phases of their subsequent cycles (Fig. 2).

Six untreated patients, having bacteriologically proved acute cervical gonorrhea and normal menstrual cycles, were hospitalized for a period of time sufficient to carry them through the duration of their current cycles and into part of their subsequent cycles. No treatment other than bed rest and sedation, if necessary, was administered. Smear examinations, cultures and pH determinations were made daily on the cervical mucus. Four patients yielded normal pH curves, and two patients yielded atypical curves.

Results of the four patients having normal pH curves:

1. During the preovulatory phase in a total of ten cultures nine were positive and one was negative.

2. Fifteen cultures were taken during ovulation all of which were positive.

3. A total of 36 cultures were taken during the postovulatory phase. Twelve of these were taken during the early part of the phase when the pH of the cervical mucus was 7.3 to 6.8; all were positive. Five cultures from the same patient were positive when the pH range was 6.4 to 6.2, but these cultures were characterized by a tremendous decrease in the number of organisms present, as evidenced by colony counts, in comparison with the number of organisms present in mucus at pH 6.8 and above. Sixteen cultures, all of which were negative, were taken during the latter part of the luteal phase (twenty-second through twenty-fifth day) when the pH of the cervical mucus was 6.4 to 5.8.

4. Premenstrual phase—two negative cultures were obtained when the pH was 6.2, and three positive cultures were obtained when the pH was 6.8.

5. Menstruation—ten positive cultures and two negative cultures were obtained during this time.

In a total of 78 cervical cultures 69.2 per cent, or 54 cultures, were positive, whereas in a total of 78 cervical smears 50.2 per cent, or 41 smears, were positive. Of 54 positive cultures, 90.7 per cent, or 49, were obtained during the estrogenic phases of the cycle and first two days of the luteal phase, when the pH of the cervical mucus was 6.8 and above.

In a total of 24 negative cultures, 70.8 per cent, or 17, were obtained during the luteal phase when the pH was 6.5 to 5.8.

All four patients had five to seven consecutive negative cultures during the luteal phase of the cycle, which were followed by positive cultures in either the premenstrual phase or during menstruation.

The two patients having atypical pH curves yielded the following results: One patient had a total of twenty cervical cultures during which time the pH range was 7.4 to 6.7. All cultures were positive. This may have been a case of anovulatory menstruation since the patient had been married for two years without any pregnancies. The other patient had a total of 27 cultures. Twenty-three consecutive cultures were negative during which time prior to the onset of menstruation, with the exception of one day, the pH was 6.6 to 5.2. On the eighth and ninth days of the subsequent cycle the cultures were positive.

Summary

In a total of 128 cervical cultures, 69.4 per cent, or 89 cultures, were positive; of these, 94.2 per cent, or 84 cultures, were positive during the estrogenic phases and the early part of the luteal phase of the cycle when the pH of the

A total of 14 patients with clinical signs of acute gonorrhea were examined during this phase. Six of these were examined on the seventeenth day of their cycles and all yielded positive cultures. The pH range of their cervical mucus was 7.4 to 6.8. Eight patients who were examined on the eighteenth through the twenty-fifth day and whose pH range was 6.6 to 5.2 yielded only negative cultures. Three of these patients had had previous positive cultures taken during menstruation and ovulation, and no treatment had been administered prior to the taking of the second cultures.

4. Premenstrual phase, twenty-sixth through twenty-eighth day. This is characterized by a withdrawal of progesterone and, according to some investigators, by a secondary rise in the estrogens. Chemically it is marked by glycogen exhaustion in the endometrium. The pH range of the cervical mucus of five patients tested during this phase was 7.1 to 6.8. Four had positive cultures and one had a negative culture.

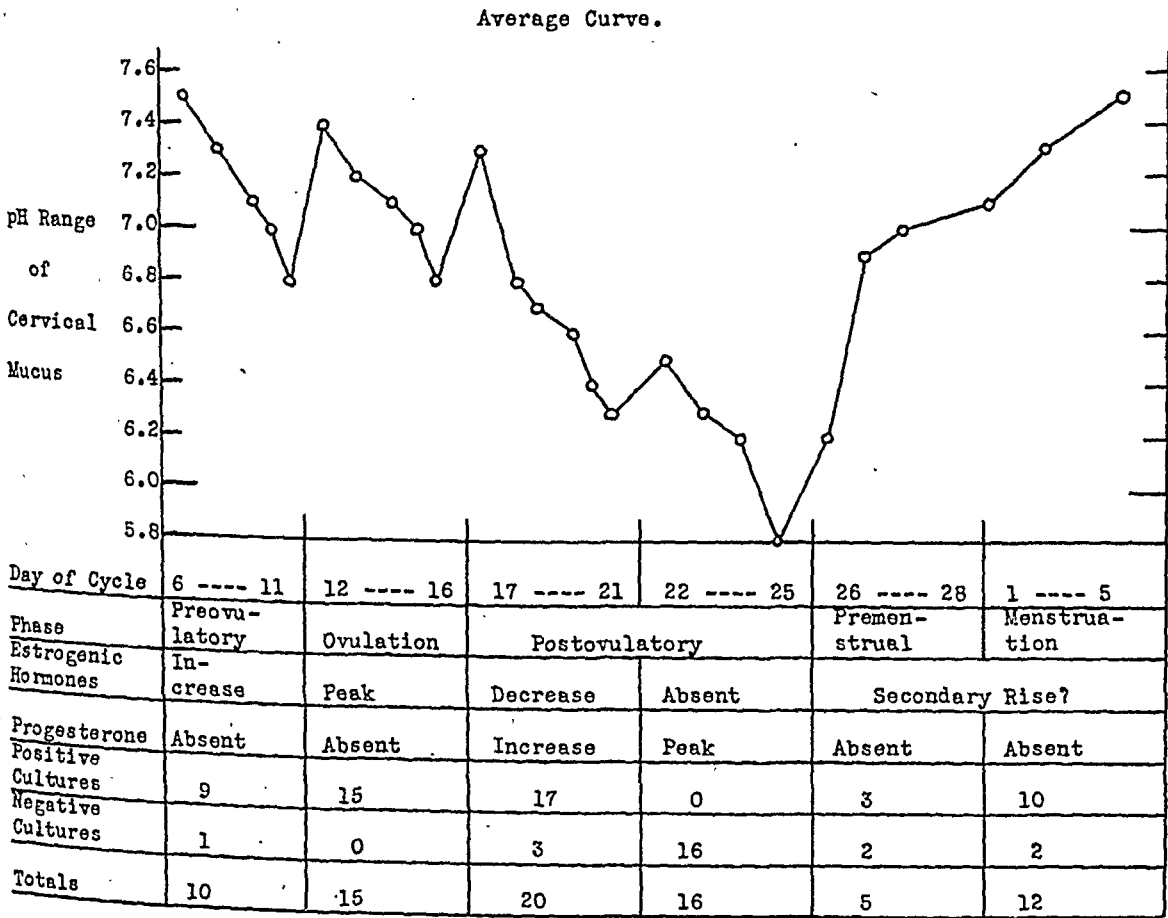


Fig. 2.—Seventy-eight cervical cultures from four hospitalized patients having bacteriologically proven acute gonorrhea, with regard to the pH of the cervical mucus and the phase of the menstrual cycle.

5. Menstruation, first through fifth day. This is characterized by sloughing off of the endometrium. At this time all hormone activity is at its lowest level and the pH of the cervical mucus is above 7.0.

Two patients examined during this phase had positive cultures. Of a total of 50 patients studied 70 per cent, or 35 cases, had positive cultures, whereas 26 per cent, or 13 cases, had positive smears. All of the positive cultures were obtained when the pH of the cervical mucus was 6.8 and above. Fifty-three per cent of the negative cultures were obtained during the postovulatory or luteal phase when the pH of the cervical mucus was 6.6 to 5.2.

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cervical mucus was 6.8 and above. Thirty-nine cultures, or 30.6 per cent, were negative. Twenty-six of these, or 66.4 per cent, were obtained during the latter part of the luteal phase when the pH range was 6.4 to 5.2.

Since smears were positive in only 54 cases, or 42.1 per cent, of the total, the invalidity of negative smears from female patients should be re-emphasized.

An investigation of the effect of low pH upon the viability of the gonococcus was tested in vitro. Pancreatic digest broth adjusted to various pH values was used as the test medium. Six freshly isolated strains reacted in the same manner. When grown in broth at pH 6.8, growth was reduced approximately 50 per cent, as evidenced by colony counts, in comparison with growth in broth at pH 7.2. At pH 6.4 and 6.0 the organism remained viable for four and two hours, respectively.

Pure crystalline progesterone incorporated in pancreatic digest broth giving a final concentration of 1 to 20,000 completely inhibited the growth of the gonococcus in two hours, regardless of the pH of the medium.

Pure crystalline alpha estradiol in a concentration of 1 to 5,000 had no visible effect upon the growth of the organism. These results agree with the studies of Faulkner,⁶ who showed that alpha estradiol in a concentration of 1 to 7,500 had no inhibitory effect upon the growth of *Neisseria catarrhalis* in vitro.

To my knowledge to date, the concentration of progesterone in the cervical mucus has not been determined, due to the lack of sufficiently sensitive tests. The activity of the corpus luteum is not measured by the activity of its biologically active hormone progesterone, but by the excretion in the urine of its biologically inactive metabolite pregnandiol. According to Venning and Browne,⁷ pregnandiol appears in the urine twenty-four to forty-eight hours after ovulation and disappears when the corpus luteum begins to retrogress two to three days before the onset of menstruation.

Conclusions

1. There is a definite correlation between the isolation of the gonococcus from cervical cultures and the phase of the menstrual cycle in which the cultures are taken.
2. Negative cultures are associated with the latter part of the luteal phase of the cycle when the cervical mucus is most acid and progesterone activity is at its height.
3. Positive cultures are associated with the estrogenic phases of the cycle when the pH of the cervical mucus is 6.8 and above.
4. Apparently several consecutive negative cultures without the knowledge of the pH of the cervical mucus at the time of culturing, does not mean absence of infection. Acid mucus is associated with negative cultures when there still may be active foci of infection possibly deep in the cervical glands.
5. Whenever possible the pH of the cervical mucus should be tested at the time of culturing. When this is not possible the date of the onset of the patient's last menstrual period should be noted when the cultures are taken.

The author wishes to thank Dr. J. Howard Brown for his constructive criticism during the course of this investigation, and to acknowledge the valuable assistance of Dr. Richard W. Telinde, Dr. Georgianna Seegar-Jones, Miss Elena Williams, and other members of the Department of Gynecology in making the clinical material available.

opposite arm. Two consecutive fifteen-minute urine specimens and a final half-hour specimen were collected. Blood was drawn at the approximate midpoint of the test.

Blood and urine urea analyses were made as described by Koch⁶ and Van Slyke and Cope,⁷ urine chlorides were measured according to the Volhard-Harvey procedure,⁸ and urine proteins were estimated by the method described by Shevky and Stafford.⁹

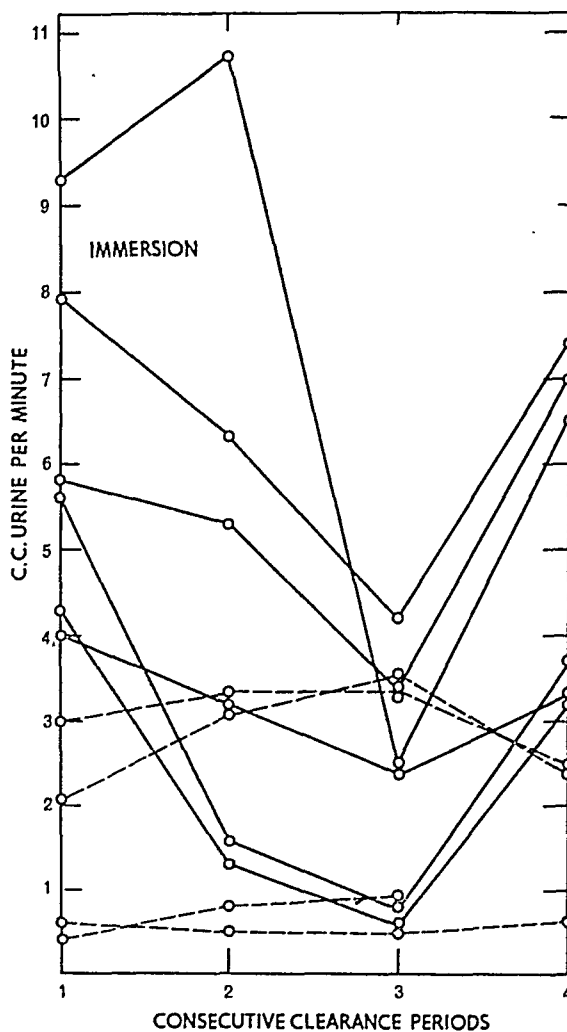


Fig. 1.—Cold pressor test and kidney function. Urine excretion per minute.

Results

In four patients who served as controls, the rate of urine excretion, urea clearance rate, U/B, chloride and protein excretion remained relatively constant during four consecutive half-hour periods.

In six of ten patients subjected to a six and one-half-minute ice immersion, a significant decrease occurred in the amount of urine collected. The decrease was reflected in a sharp decline in urea clearance rate and chloride excretion/minute and in an increased U/B ratio. In four of this group a proteinuria followed immersion. The blood pressure rose appreciably in five patients. The maximum systolic rise varied between 33 to 70 mm. Hg, diastolic 22 to 28 mm. Hg. In one case there was no significant change in blood pressure.

COLD PRESSOR TEST AND KIDNEY FUNCTION*

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THE vascular response to the cold pressor test consists of a rise† or, rarely, a fall in systolic and/or diastolic blood pressure.^{1, 2} In addition, vasospasm,^{3, 4} a proteinuria, and a decreased endogenous creatinine clearance rate⁵ have been detected during and following the test. The last two findings, associated with a rise in blood pressure, have been interpreted as being due to the effect of vasospasm within the kidney.⁵ The present study reports the effect of a prolonged (six and one-half minute) cold pressor test on blood pressure and renal function.

Materials and Method

A total of 14 pregnant and nonpregnant women were selected for study. Of these, all but one of the former had evidence of pregnancy toxemia, and all of the latter had a positive history of hypertension.

From 6 A.M. until completion of test, the patient drank 200 c.c. of water every one-half hour. An inlying catheter was used to obtain urine specimens, and air was injected into the bladder at the conclusion of each clearance period to insure complete emptying.

Three consecutive half-hour specimens, relatively equal in volume, were obtained. The first two were discarded and the third was retained as representative of the control period. The patient's hand was then immersed in ice water for six and one-half minutes, the blood pressure being obtained from the

TABLE I. COLD PRESSOR TEST AND KIDNEY FUNCTION EFFECT ON BLOOD PRESSURE
AND URINE PROTEIN EXCRETION

| PATIENT | MAXIMUM RISE SYSTOLIC BLOOD PRESSURE MM. HG | MAXIMUM RISE DIASTOLIC BLOOD PRESSURE MM. HG | MG. PROTEIN PER MINUTE URINE CLEARANCE PERIODS | | | |
|---------|---|--|---|------|------|------|
| | | | 1 | 2 | 3 | 4 |
| 239868 | 40 | 32 | 0 | 0.13 | 0.13 | 0 |
| 376640 | 50 | 30 | 0 | 0.77 | 0.18 | 0.46 |
| 378732 | 30 | 30 | 0 | 0 | 0 | 0 |
| 375166 | 40 | 22 | 0 | 0 | 0 | 0 |
| 385336 | 70 | 38 | — | — | — | — |
| 245483 | 8 | 0 | 0 | 0.13 | 0.08 | 0 |
| 376050* | 10 | 16 | 0 | 0 | 0 | 0 |
| 376091* | 28 | 20 | 1.16 | 1.69 | 1.18 | 1.82 |
| 246828* | 26 | 24 | 0.16 | 0.17 | 0.16 | — |
| 240186* | 20 | 20 | 0.13 | 0.22 | 0.25 | 0.19 |

*Patients exhibiting no decrease in urine volume as a result of ice immersion (broken lines in Figures 1, 2, and 3).

*Supported by Chicago Lying-in Fiftieth Anniversary Research Fund on Eclampsia.

†Twenty-two mm. Hg systolic is considered the upper limit for a normal increase in non-pregnant individuals (1); 29 mm. Hg during pregnancy (2).

tissues. He attributed the antidiuresis after such a stimulus to a posterior pituitary effect.

The administration of solution of posterior pituitary to pregnant patients results in an antidiuresis and a relative increase in chloride excretion.¹² Whether the suppression and the decline (per minute) in urine chlorides following ice immersion involves pituitary action requires further investigation. A higher maximal increase in systolic and diastolic blood pressure was noted in cases exhibiting urine suppression, and a proteinuria followed immersion in three of five such patients (Table I). These facts suggest an altered filtration rate, possibly the result of vasospasm, as an underlying mechanism.

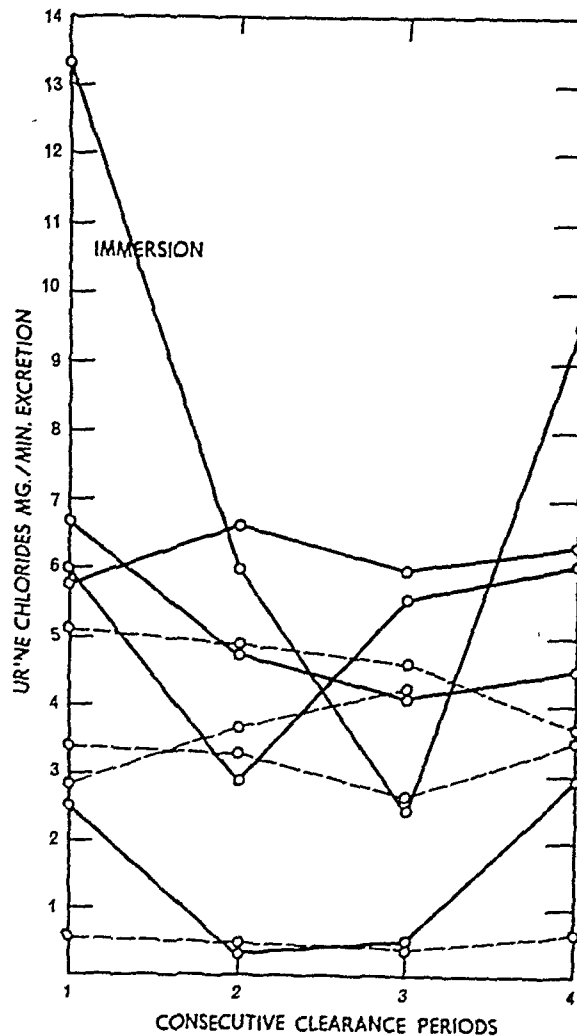


Fig. 3.—Cold pressor test and kidney function. Chloride excretion per minute.

Summary

Under constant conditions of water intake and urine excretion the immersion of one hand to the wrist in ice water may reduce the urine collected per minute, the urea clearance rate, and the renal excretion of chlorides per minute. This phenomenon may be associated with an increase in urine protein excretion. Those patients not responding to the ice water stimulus tended to have a lower urine volume or urea clearance rate initially, and exhibited a less pronounced increase in systolic and diastolic blood pressure.

In the four remaining patients no changes were observed in urine collected following exposure to ice water. This group was characterized by an initial low urea clearance rate, and, in two instances, by a relatively low urinary output. The blood pressure, however, increased 20 to 28 mm. Hg systolic and 16 to 24 mm. Hg diastolic (Figs. 1, 2, and 3, and Table I).

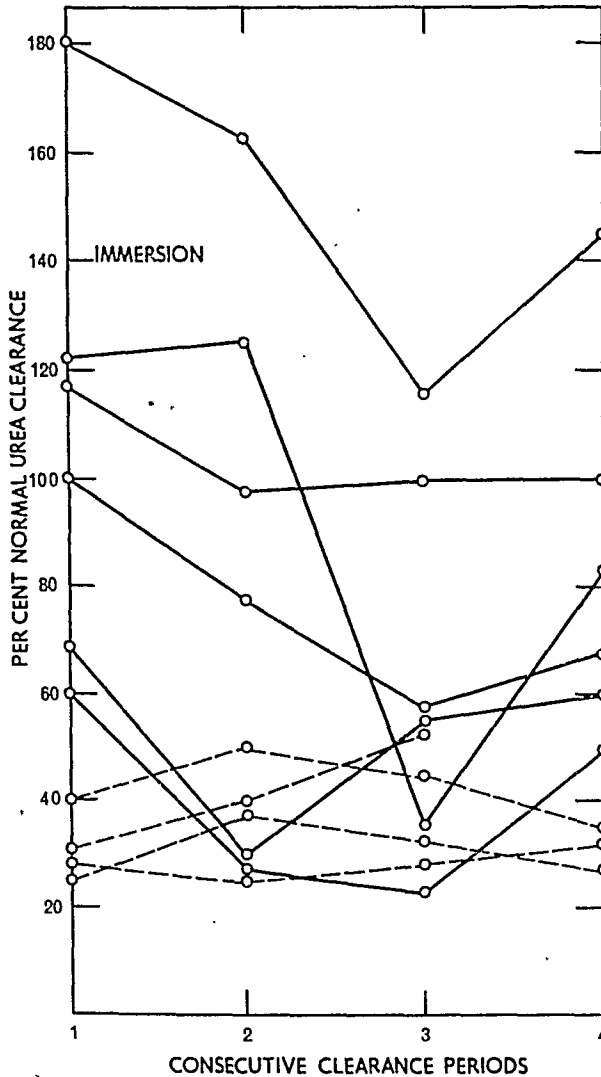


Fig. 2.—Cold pressor test and kidney function. Urea clearance; per cent normal.

Comment

Changes in the volume of urine excreted depend upon either the filtration rate or rate of tubular reabsorption, or both. Among the factors influencing the former are: variations in filtration surface (number of functioning glomeruli), and changes in intracapsular pressure, renal blood flow or plasma protein content; tubular reabsorption depends upon the rate of urine flow through tubules) as well as upon the antidiuretic effect of the posterior pituitary gland. Either mechanism would explain a suppressed excretion following ice immersion.

Wolfe¹⁰ obtained variable figures for renal blood flow and glomerular filtration (using diodrast and inulin) following cold exposure, but observed a sharp depression of both functions after other painful stimuli. Verney,¹¹ however, using a thermostromuhr on the denervated dog kidney, recorded only a transient fall in renal blood flow following an electrical stimulus to subcutaneous

A NEW RULE FOR CORRELATING THE AGE OF HUMAN FETUSES WITH SIZE IN INCHES*

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IN AN attempt to simplify more complicated formulas (e.g., Henri and Bastien, 1904; Scammon, 1921) of use in computing the age and size of human embryos, Scammon and Calkins (1923) have published empirical formulas which, though far simpler, cannot be kept in mind with any ease and cannot be carried out as a mental calculation. These particular formulas apply to fetuses between 3 and 10 months old and are in terms of crown-heel (standing height) values only. Noback (1922) has shown how to derive either crown-heel length from crown-rump length (sitting height) during the fetal period, or the reverse.

Familiar working rules are those of Haase (1875), which state that for the first five fetal months the total length in centimeters (crown-heel or standing height) equals the square of the month, whereas in the last five fetal months it equals the number of the month multiplied by five. The results gained from these calculations fit the actual measurements rather closely. In order to obtain greater flexibility and range, the present writer (1925) proposed equally simple formulas that could be employed to calculate age from metric length or metric length from age; the measurement of length used could be expressed either in standing- or sitting-height values. These latter formulas have enjoyed a degree of popularity and have been incorporated in textbooks both in this country and in Europe.

From the standpoint of a student or practitioner living in an English-speaking country, there is some advantage in a rule that is based on inches, rather than on centimeters as hitherto has been the case. The plain fact remains that few individuals in this country, at least, think or estimate well in metric values. With this in mind, the attempt was made to devise a simple rule that could be easily remembered and readily applied to estimates or measures of fetal length in inches.

The chief difficulty in producing any kind of simple formula is the fact that the growth rate of a fetus is not uniform throughout the period of gestation. In the first five months it is decreasing rapidly, whereas in the last five months it is nearly constant. This means that actually there must be two rules, if the two sets of conditions are to be met without resorting to an unwieldy mathematical formula that combines both into a single expression. The last half of gestation presented no difficulty since the constant 5, used by Haase for centimeter values, converts directly into 2 when using inches (1 in. = 2.54 cm., or 2 in. = 5.08 cm.). On the other hand, the rule for the first half of gestation was obtained only after numerous attempts on a trial-and-error basis had been made. The new rules for calculating the greatest length in inches of an embryo or fetus at any lunar month are as follows:

For the first five lunar months, add the numbers of the preceding months.

Examples: At 1 month = 0 inch
At 3 months, $1 + 2 = 3$ inches
At 5 months, $1 + 2 + 3 + 4 = 10$ inches

For the last five lunar months, multiply the number of the month by two.

Examples: At 6 months, $6 \times 2 = 12$ inches
At 10 months, $10 \times 2 = 20$ inches

*Contribution No. 476 from the Anatomical Laboratory, Northwestern University Medical School.

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ADVANCED ABDOMINAL PREGNANCY

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ADVANCED abdominal pregnancy is so rare that only a few clinicians encounter an occasional case. For this reason it is interesting that within a period of two months the three cases reported here should have been seen in a single hospital.

In treating the cases, two practical questions arose to which answers were not easily found in the literature. These were (1) the length of time required for the placenta to become avascular when left in the abdomen after the death of the patient or removal of the fetus, and (2) the time necessary for absorption of the retained placenta.

In the individual case the time at which the placenta becomes avascular can be determined by a pregnancy test. Eisman and Ziegler had a case in which the child was living at operation and the placenta was left intact. Eight days later the Aschheim-Zondek test was negative. MacGregor's patient had a negative test ten days after removal of the fetus. On the other hand, in the first case reported here, the Friedman was positive on the fifty-third postoperative day and became negative on the fifty-eighth. A patient of Hart had a positive test one hundred days after fetal movements were last felt. Lull had a patient on whom the Friedman was positive on the forty-fifth postoperative day. At laparotomy fifty-six days after the original operation, the placenta was necrotic. He suggests that if the patient is first seen after death of the fetus three to four weeks be allowed to elapse before operation, if her condition warrants. This gives a reasonable time in which separation and necrosis of the placenta may proceed, and makes the possibility of safe removal of the placenta more likely. The patient should be watched during the time for evidence of abdominal hemorrhage or infection.

The second question which arose was the length of time required for absorption when the placenta is left in the abdomen. When not removed the placenta may absorb, it may liquefy, or it may suppurate. Suppuration requires surgical drainage. However, drainage of the mass, as would be expected, hastens its disappearance. When there is no suppuration, there is usually no pain nor discomfort, but resolution of the placental mass takes months or even years.

In the second of our cases liquefaction without suppuration took place. Eight months after operation the mass was the size of a six months' uterine pregnancy. MacGregor reports a similar case in which at the end of sixteen months the sac was the size of an orange. A patient seen by Mason had a residual mass two inches long after five months. Studdiford has seen a case in which at the end of thirteen months a pelvic mass was still felt, while Jewett's patient had a small residuum two and one-half years after operation. In none of these patients was there any abdominal discomfort.

CASE 1.—The patient was a Negro woman 28 years of age, who had had no previous pregnancy. Her last menstrual period was Nov. 25, 1945. On January 20 she developed lower abdominal pain. The pain was not knifelike, and she did not faint, but after two days of the pain she developed moderate vaginal bleeding which persisted for eight days. There was no further pain nor bleeding. Fetal movements were felt about April 20.

It is believed that these rules have much to commend them in simplicity, convenience, and accuracy. The computations obtained represent the total length, including the straightened legs when present; actually the legs are present and increase the greatest length in all months except the first. In practice it makes no difference which rule is used at five months, since $1 + 2 + 3 + 4 = 10$ and $5 \times 2 = 10$. When formulating the rules it seemed that memory might be aided better if the period of intrauterine development were broken into exact halves consisting of months 1 to 5 and 6 to 10.

The same rules can be used in reverse for the purpose of calculating age from size. The age of any fetus more than 10 inches long is one-half its total length in inches. The age of fetuses less than 10 inches long can be found by matching fetal length to the nearest sum obtained by the addition of month numbers, as already explained. It is clear that the age must be one month more than the highest month number used in the successful match. All this is much simpler than it sounds. For example, a 6-inch fetus matches $1 + 2 + 3$ months, and hence must be four months old.

The closeness of fit of the results obtained by these empirical formulas to the actual measures of crown-heel length can be seen in the appended tabulation. For purposes of comparison, the percentages of error in the calculations obtained by using Haase's rules have been added as a last column of the table. No entry has been made for the percentage error at one month when using the new rule; this is because it is meaningless to record the error as infinite when it is only 0.2 inch from being correct.

TABLE I.

| AGE IN LUNAR MONTHS | CROWN-HEEL LENGTH IN INCHES | CALCULATED CROWN-HEEL LENGTH | PERCENTAGE ERROR OF CALCULATION | PERCENTAGE ERROR, USING HAASE'S RULE |
|---------------------|-----------------------------|------------------------------|---------------------------------|--------------------------------------|
| 1 | 0.2 | 0.0 | | +100 |
| 2 | 1.2 | 1.0 | -17 | + 33 |
| 3 | 2.9 | 3.0 | + 3 | + 23 |
| 4 | 6.2 | 6.0 | + 3 | + 2 |
| 5 | 9.4 | 10.0 | + 6 | + 5 |
| 6 | 11.7 | 12.0 | + 3 | + 1 |
| 7 | 14.0 | 14.0 | 0 | - 1 |
| 8 | 16.1 | 16.0 | - 1 | - 2 |
| 9 | 18.0 | 18.0 | 0 | - 2 |
| 10 | 19.8 | 20.0 | + 1 | 0 |

Summary

Empirical formulas, expressed as two easily remembered rules, have been presented by which fetal age and fetal size in inches can be readily correlated through a simple mental calculation. The conversion can proceed from age to size or from size to age.

Any error resulting from the use of these rules is less than the error that would ordinarily occur in measuring a specimen.

The fit of these formulas is somewhat better than that obtained from the use of Haase's rules, and the reliability of the latter is very good indeed.

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On August 24 the necrotic placenta was removed. The opening in the sac had sealed over, and the persistent discharge was coming from the abdomen and not the sac. On incising the sac about 30 c.c. of thick pus poured out. Five grams of sulfanilamide powder were sprinkled into the sac and three Penrose drains inserted, which were removed on the third day. On the sixth day the patient complained of rectal pain, her temperature was 100° F., and a cystic tender mass the size of a golf ball was felt in the cul-de-sac on vaginal examination. A posterior colpotomy was done under local anesthesia, and about 40 c.c. of pus were released.

The patient's recovery following this was uneventful. There was a diminishing purulent discharge from the abdominal incision for eight weeks following the operation. When seen four months after operation, the patient looked well and had no complaint. On pelvic examination, a slightly tender mass the size of a ping-pong ball could be felt in the right fornix. No other pelvic abnormality was made out.

CASE 2.—The patient was a 36-year-old woman, gravida vii para iii, who entered the hospital on June 27, 1946. Her last menstrual period was about August 20, ten months before admission. On October 2, when rising from her chair, she developed a sharp pain in the right lower quadrant and had to be carried to her bed. For the next three days she had a spotting of bright red blood. There was no further vaginal bleeding until the day before admission when there was again a small amount of bright red blood.

The patient was not well from the time of her first attack of pain until her admission to the hospital. She had frequent attacks of vomiting, faintness, and abdominal pain. She was seen by several different doctors who thought that she was having threatened abortion or had a pelvic infection along with a uterine pregnancy.

The first fetal movements were felt in December. As soon as movements became vigorous (about January 10) they were accompanied by so much pain that the patient could not sleep. The movement was always on the right side of the abdomen. Fetal movements were last felt on May 22.

On June 26, the patient developed pain in the right lower quadrant and a little bright vaginal bleeding. She was admitted to the hospital in good general condition on the following day. Red blood cell count was 3,440,000; hemoglobin, 71 per cent; Rh negative. The abdomen was enlarged to the size of a ten months' pregnancy, but felt very nodular. Fetal small parts were easily made out. No fetal heart tones were heard. X-ray showed the fetus in transverse position. A diagnosis of abdominal pregnancy with a dead fetus was made, and operation was decided upon.

Operation was performed on June 30, 51½ weeks from the day fetal movements were last felt.

On opening the peritoneal cavity a small amount of dark prune-juice colored fluid appeared. A macerated fetus about the size of a seven months' gestation was found lying in its membranes. The sac was opened through the membranous area, and the placenta avoided entirely. The placenta was attached to the posterior abdominal wall, the small intestine, and the posterior surface of the right broad ligament. There was a thick layer of fibrin on that portion of the placenta which could be seen. The placenta showed a mottling of necrosis with about half of the organ still vascular. No attempt was made to remove the placenta. The infant was delivered and the cord was cut short and tied. The abdomen was closed without drainage.

The patient's postoperative course was uneventful. During the first eleven days there was an elevation of temperature to from 100.8° to 99.4° F., after which there was no further fever.

The patient was first seen on May 20. She had no complaint. The abdomen had the appearance of an eight months' pregnancy, but enlargement on the right was more prominent than on the left. Small parts could not be palpated. The fetal heart tones were heard in the left lower quadrant.

On vaginal examination the cervix was soft. The fundus could not be outlined, and pressure on the abdominal mass from above did not cause movement of the cervix. On rectal examination a cystic mass could be felt extending into the cul-de-sac. Small parts were felt in this mass. When an extremity in the cul-de-sac was caught by the examining fingers it moved vigorously. X-ray showed a seven months' fetus in transverse position. No placenta shadow could be seen. A diagnosis of abdominal pregnancy was made, and immediate operation advised.

On opening the abdomen on May 23, a bluish glistening mass was found filling the lower abdomen and extending three fingerbreadths above the umbilicus. The mass was adherent to the small intestines above, and to the posterior surface of the uterus below. As there were no adhesions to the anterior surface of the sac, and as the surface here was glistening, this area was thought to be made up of membranes only, and a longitudinal incision was made through it. The entire incision went directly through the underlying placenta which was about one-half inch in thickness.

Due to the necessity to complete the operation as soon as possible because of bleeding, no further investigation of the relationship of the pelvic organs to the sac was made. After the operation was completed, it was realized that the fact that the sac had a complete peritoneal envelope meant that rupture of the original tubal pregnancy had taken place into the broad ligament on the left and that the fetus and fetal products were contained between the leaves of the ligament.

At operation on opening the sac there was a gush of amniotic fluid, and a live seven months' female infant was delivered. The child died two hours later. Autopsy revealed no anomalies.

Bleeding from the cut edges of the placenta was profuse but was controlled by ring forceps, which were carefully replaced by sutures. Manipulation, however, had started bleeding from the placenta deep in the sac. Two two-yard gauze packs were used to check the bleeding. The abdomen was closed, space being left only for the exit of the gauze drains.

The patient left the table with a blood pressure of 80/0. She had received 500 c.c. of blood on the operating table, and was given an additional 1,000 c.c. during the next thirty-six hours. On the second postoperative day the drains were gently loosened, and about one foot of each removed. This procedure was repeated daily until all of the pack had been removed by the seventh day. Blood was kept in readiness for immediate transfusion in the event of a postoperative hemorrhage, but at no time was there any fresh bleeding. The patient, however, developed a rather free dark brown discharge from the wound. She left the hospital on the sixteenth day. At that time her hemoglobin was 65 per cent and she had no elevation of temperature.

Three weeks after delivery a little milk appeared in the breasts. A week later she passed a large sheet of decidual tissue. Seven weeks after operation the patient developed a moderate grade fever and abdominal pain, and on examination showed a mass the size of a grapefruit near the umbilicus. She was readmitted to the hospital. Chemotherapy largely controlled the fever, but the pain persisted and the abdominal mass increased in size. A Friedman test on August 8 was positive. On August 13, fifty-eight days after removal of the infant, it became negative. The brown discharge from the abdominal wound had persisted and, in spite of iron and liver by mouth, an occasional transfusion was necessary to keep the patient's hemoglobin to a level of 60 per cent.

could not be obtained, but it was thought that due to the rent in the posterior wall of the sac the pack was not effective and that the patient died of internal hemorrhage.

The infant had no evidence of any defect, and three months after delivery is living and well.

I wish to express my thanks to Dr. J. H. Williams for allowing me to present the second of these cases.

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She was discharged on the nineteenth postoperative day. At that time there was a rounded mass in the abdomen that reached 3 cm. above the umbilicus.

The patient was seen at frequent intervals following this. She had no complaint, and normal menstruation was resumed. The mass gradually decreased in size, but seven months after operation it still extended one fingerbreadth above the umbilicus and dipped into the pelvis below. It was about 10 cm. long and 6 cm. across. The fundus was average size and could be felt anterior to and adherent to this mass.

CASE 3.—The patient was a Negro woman 31 years of age, gravida i, para 0, whose last menstrual period was July 10, 1945. Five weeks later she developed a scant bloody discharge, had severe lower abdominal pain, and fainted.

During the fourth month there was a return of this pain and the patient was admitted to the hospital on November 9. Her temperature was 100° F., pulse 88, white blood cells 5,800, and hemoglobin 57 per cent. The uterus extended three fingerbreadths below the umbilicus, and a tender mass was felt in the left fornix and extending into the cul-de-sac. A diagnosis of uterine pregnancy and acute salpingitis was made. With chemotherapy the fever subsided and after receiving 500 c.c. of blood the patient was discharged on November 19.

Twice during the next six weeks she was readmitted for colicky pain, nausea and vomiting, abdominal distention, and obstipation. An x-ray of the abdomen showed multiple fluid levels in the intestines, and a diagnosis of intestinal obstruction was made. The condition responded promptly to the use of a Miller-Abbott tube, but after relief of the obstruction there was a tendency for recurrence of the attacks of abdominal pain. On one of these occasions the patient again fainted.

On April 10, nine months after the onset of the last menstrual period, the patient developed rhythmic pains and was admitted to the obstetric ward. The abdomen was enlarged to the size of a term pregnancy, and fetal heart tones were heard in the right lower quadrant. Small parts could not be outlined. The cervix was long and the os closed. Posterior to the cervix a firm mass about 6 cm. in diameter could be felt. Anterior to the cervix two smaller nodules could be felt. A diagnosis of uterine pregnancy at term with uterine fibroids blocking the pelvic outlet was made. It was decided that delivery should be done by cesarean section. Five hundred cubic centimeters of blood were given before taking the patient to the operating room.

On opening the abdomen a large oval mass which was thought to be the pregnant uterus was found. This was opened, and a 2½-pound living male child was extracted without difficulty. It was then seen that the mass was not the uterus but the sac of an abdominal pregnancy. The sac showed a rent in its posterior wall and its cavity contained several old organized blood clots. The placenta was adherent to the transverse colon, small intestines, and posterior abdominal wall. The fundus was the mass that had been felt in the cul-de-sac before operation, and it showed two fibroid nodules on its anterior wall.

At operation the fetal sac had been opened through a part of the placental site, and bleeding here was free. No attempt was made to remove the placenta, but there was profuse bleeding from the depth of the sac. Three five-yard gauze rolls were pushed into the sac, and the edge of the sac anchored to the peritoneal edges. The abdomen was closed, allowing space only for the exit of the drains.

The patient's condition was poor during the operation. She received stimulants and 1,250 c.c. of blood while in the operating room. On leaving the room her blood pressure was 75/30, pulse 120. She was treated for shock but did not respond, and died four hours after operation. Permission for autopsy

time in the breast milk, using the methods of Witebsky, Anderson, and Heide.¹⁷ Agglutinins were observable again in the maternal serum one month after delivery, demonstrable in the undiluted serum, but six weeks from the child's birth all Rh antibodies had disappeared from the maternal circulation.

CASE 2.—Mrs. A. L., was Group O, Rh negative. The husband was Group A, Rh positive. The history includes one living and well child, 5 years old, not available for tests, and one miscarriage at four months which occurred two years after the birth of the first child. Baby L. was born after a five-hour labor, a female child, Group A, Rh positive. Blood findings on the third day of life showed red blood cells, 5,320,000; white blood cells, 10,200; hemoglobin 15.5 Gm., erythroblasts 2/100 white blood cells. Except for a very slight jaundice, the baby progressed normally. Neither liver nor spleen was enlarged. The child was artificially fed. Agglutinins were demonstrable in the baby's blood, with no blocking antibodies observable; this work was done on the same day as the blood counts.

When six months pregnant, Mrs. A. L. had weak blocking antibodies in undiluted serum. These persisted without apparent increase in strength and at delivery at term, both anti-Rh agglutinins and blocking antibodies were found in the maternal serum. Blocking antibodies were present in a 1:3 dilution, and agglutinins could be demonstrated in a 1:10 dilution, using titration methods. Undiluted breast milk agglutinated Group O, Rh positive cells. At six weeks after delivery, agglutinins had disappeared; blocking antibodies were still present in undiluted serum.

CASE 3.—Mrs. L. R., Group A, Rh negative. Her husband was Group AB, Rh positive. There was one living child, a normal 10-year-old, by a former husband. This child was Group A, Rh positive. There were two miscarriages, both at two months, one five years and one seven years after the birth of the first child. Baby R. was born after a six-hour labor, a female child, Group B, Rh positive. Blood findings one day after delivery showed red blood cells 4,120,000; white blood cells, 11,150; hemoglobin, 15 Gm.; erythroblasts 4/100 white blood cells. Except for slight jaundice, the child progressed normally, with no other findings suggestive of hemolytic disease except the low red cell count. The maternal blood showed agglutinins through a 1:3 dilution of serum, with no blocking antibodies, six weeks before delivery. These were present, but in no higher titer three days after delivery, but had disappeared in six weeks. Breast milk was not tested.

CASE 4.—Mrs. M. G., was Group B, Rh negative. The history had no miscarriages. The husband was Group B, Rh positive. Two older children, a three-year-old girl and a five-year-old boy, were both Group B, Rh positive. Baby G., a male child, Group B, Rh positive, was born after an eleven-hour labor. One day after delivery the blood findings were red blood cells, 5,920,000; white blood cells, 14,800; hemoglobin 18 Gm., erythroblasts 35/100 white blood cells. Hepatomegaly and splenomegaly were not demonstrable. The child showed slight jaundice, but appeared otherwise normal and was dismissed from the hospital with the mother. Artificial feeding was given from the beginning.

There was no evidence of maternal Rh sensitization during pregnancy. Two days after delivery, anti-Rh agglutinins were present in the mother's blood, demonstrable in undiluted serum only. There was no blocking reaction apparent. Agglutinins were found in undiluted breast milk and could be recovered from the child's blood. Evidence of sensitization did not persist to the six weeks' period.

MATERNAL RH SENSITIZATION AND THE CLINICALLY NORMAL CHILD

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SINCE the Rh factor was first described⁶ and its relationship to erythroblastosis fetalis noted,¹⁰ comment has arisen as to the discrepancy between the number of instances of Rh-negative mothers with Rh-positive children (one out of ten pregnancies) and the incidence of erythroblastosis fetalis (one case in 200 deliveries). Various suggestions have been offered to account for this discrepancy; the following are examples: relative permeability of the placenta (Levine^{7,8}), size and combining powers of types of Rh antibody (Wiener^{13, 14, 16}), susceptibility of the individual to isoimmunization, the constitutional factor K, postulated by Wiener,¹⁶ competition of isoagglutinins (Wiener¹²), and the mother's history as regards transfusion (Levine⁹). As an additional factor, it may be suggested that cases are present in which mothers show transitory agglutinins and in which the babies show slight or no apparent damage; these cases are probably largely overlooked in the course of a busy obstetric practice.

Six cases of maternal sensitization with no evidence of erythroblastosis fetalis in the child have been observed in the Western Pennsylvania Hospital during the two years since the inauguration of the Blood Grouping Laboratory. In this period there have been 3,290 deliveries, 337 Rh incompatibilities between mother and child, and 18 cases of recognizable erythroblastosis fetalis. In each of the six cases mentioned, there was nothing apparent to suggest congenital hemolytic disease, yet in each case there was a period near the time of delivery when maternal sensitization to the Rh factor was demonstrable. Four of these cases are detailed below.

Report of Cases

CASE 1.—Mrs. I. T., was Group A, Rh negative. Her husband was Group AB, Rh positive. A 3-year-old son was Group A, Rh positive. A 5-year-old daughter was not available for tests. Both children were normal. Baby T. was a female child, Group A, Rh positive, born after a three-hour labor. There had been no miscarriages. The blood findings on Baby T. two days after birth showed red blood cells, 6,180,000; white blood cells 9,700; hemoglobin, 17 Gm., erythroblasts 30/100 white blood cells. Agglutinins were demonstrable in the baby's blood according to the method of Carter and Loughrey.¹ No blocking antibodies (Wiener¹⁵) were found. There was no appreciable jaundice or pallor, and neither hepatomegaly nor splenomegaly was apparent. The baby progressed normally, with artificial feeding, and left the hospital with the mother.

Two days after delivery, agglutinins demonstrable in the undiluted serum were found in the mother's blood. Anti-Rh agglutinins were found at the same

in pregnancy. Levine and co-workers^{10, 11} believe that failure of the development of clinical hemolytic disease in the child of a demonstrably sensitized mother is due to a relatively short duration of intrauterine exposure to antibody. However, one of our cases showed demonstrable antibody when six months pregnant.

Since observation of the cases detailed above, none of the four women described has given birth to a child, although one is five months pregnant. It is interesting to speculate as to what the outcomes of future pregnancies may be. If the capacities of the child to resist the harmful effects of maternal antibodies are temporary with the individual, it is possible that later pregnancies with Rh-positive infants will end in hemolytic disease, since the mother had already become sensitized. However, if the relative resistance of the child involves a genetic characteristic, it is possible that future pregnancies will also have a satisfactory outcome.

In summary, four cases of maternal sensitization to the Rh factor are presented in which clinical manifestations of congenital hemolytic disease failed to develop in the children. It is suggested that this may not be an unusual phenomenon. Various theories are reviewed in an attempt to explain these findings.

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Discussion

Each of these four cases has in common the agglutination of the child's cells and of Group O, Rh-positive cells by the serum of the mother, which ordinarily is diagnostic of sensitization of the mother to the blood of the Rh-positive child. In each of the two cases in which there was a discrepancy of the blood groups between the child and the mother, the mother's serum was titrated against appropriate cells to rule out isoimmunization against one of the blood groups. In no case was a high titer found: the highest was four plus in a 1:40 dilution. Maternal serums were tested for isoimmunization, using a number of different methods: the range was from the agglutinin tests and those for blocking antibodies through the newer methods employing albumin suspended cells. Each mother proved to be sensitized to the Rh factor when the serum was tested against cells suspended in an albumin medium, as in the methods of Diamond and Denton.² None of these mothers had received transfusions for any reason.

Dockeray and Sachs³ have reported cases in which maternal antibodies to Rh were demonstrable without clinical evidence of erythroblastosis fetalis in the child. Goldbloom and Lubinski⁴ have cited a similar case in their experience. Kariher and Miller⁵ have presented two such cases. It is probable that these instances are more common than is generally recognized, but that they do not come to the attention of the clinician or the laboratory.

Since both blocking antibodies and regular agglutinins are involved in this series, the failure of clinical hemolytic disease to develop in the children cannot be ascribed to the lack of one or another type of antibody. The choice would seem to lie between a theory of inaccessibility of maternal agglutinins to the baby's red cells, on the one hand, or, on the other, the postulate that the child is relatively immune, whether passively or actively, to the maternal antibody. As regards the first alternative, this is the theory favored by Dockeray and Sachs³; they suggest that antibodies pass the placental barrier only under certain conditions. However, in three of the four cases which we have considered above, antibodies to Rh were demonstrable in the child's blood. As concerns the second theory, it is possible that individual infants may vary in their ability to withstand the hemolytic or agglutinative effects of the maternal antibodies: that the infant blood may be protected, either through the lack of some substance necessary to complete the antigen-antibody combination or through the presence of a protective element. Kariher and Miller⁵ suggest that the secretion or nonsecretion of Rh substance by the child's tissues may be significant as regards maternal sensitization. Theoretically, if the child were a secretor of Rh substance the antibodies would be neutralized by this material as found in the fetal tissue cells, and thus much of the pressure removed from the child's red blood cells. Wiener has suggested that "X protein"¹⁶ may be the factor involved in the severity of congenital hemolytic disease. According to this concept, the stage of development of the child's serum proteins influences the outcome of the Rh negative—Rh positive incompatibility

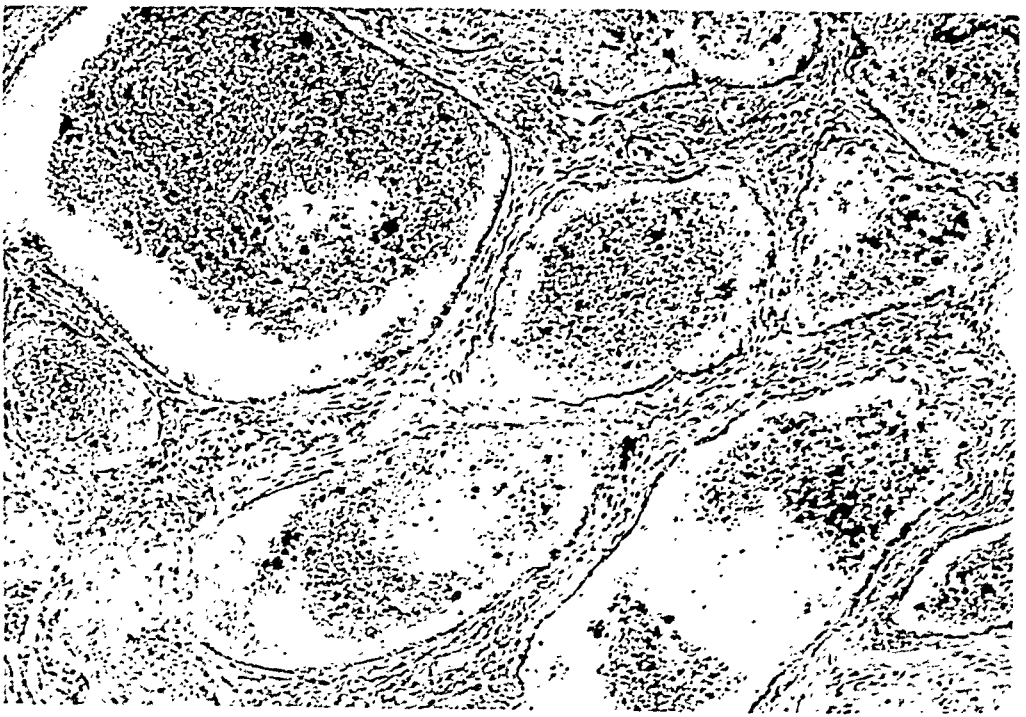


Fig. 1.—Showing dilated, thin-walled blood vessels surrounded by dense fibrous connective tissue. (X80.)



Fig. 2.—A, Thickened blood vessel walls containing smooth muscle fibers. (X80.)
 B, Showing replacement of stroma of the papillary process of the mucous of the Fallopian tube by numerous thin-walled blood capillaries.

CAVERNOUS HEMANGIOMA OF THE FALLOPIAN TUBE

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CAVERNOUS hemangioma of the Fallopian tube has, to our knowledge, never been reported in the literature. Although hemangiomas are seen quite frequently, particularly in the skin, the infrequency with which they are encountered in the uterine adnexa makes this case worth while to be presented in the literature.

Schnedorf,¹ in a review of 205 cases of tumors of the round ligament, included a hemangioma which, according to him, was the first hemangioma of the round ligament to be reported. Orth² has reported a case of multiple congenital hemangiomas in both ovaries, skin, and other organs of a child. Gottschalk³ described a case of diffuse bilateral cavernous transformation in both ovaries. Braithwaite⁴ also reported a case of angioma of the ovary.

Case Report

A 28-year-old white woman, para i, gravida i, was admitted to the Cook County Hospital on Oct. 18, 1937, with complaints of lower abdominal pain for three months and dysmenorrhea for one year. For the past ten years, since marriage, there had been a brownish, nonodorous, scanty discharge.

Physical examination was essentially negative except for the pelvic examination which revealed a firm, pea-sized, whitish nodule on the left labium minor, also adnexal tenderness bilaterally, especially on the left side where a suggestive mass was palpated.

The clinical impression was that of tubo-ovarian disease and endocervicitis. On Oct. 24, 1937, the patient was operated upon, and a high defundectomy, a left salpingo-oophorectomy, and an appendectomy was performed.

Pathologic Findings: The specimen consisted of a fundus of a uterus, left tube and ovary, and appendix. The amputated portion of the uterus measured 3.5 by 4.5 by 2 cm.; the wall was 16 mm., thick, pale purplish-gray in color. The endometrium was 2 mm. thick and purplish-tan in color. The fimbriated end of the Fallopian tube was patent, the wall was tortuous, and the mucosa was dark purplish-gray. Attached to the mucous membrane of the tube, near the fimbriated end, was a polypoid mass which measured 1.5 by 1.5 by 1 cm. This mass was dark purplish red mottled by areas of greyish white, and appeared to fill the entire lumen of the tube. The ovary measured 3 by 2.2 by 1.5 cm. and on sectioning contained single follicular cysts up to 8 millimeters.

Microscopic sections were made of the nodule protruding into the lumen of the Fallopian tube including the wall of the tube. The microscopic picture revealed the node to be composed of large, dilated, cavernous vessels filled with red blood cells which replaced the stroma of many of the folds of the fimbriated end of the Fallopian tube. Many of the vessels were thin-walled and surrounded by an ample amount of dense fibrous connective tissue (Fig. 1). Some of the vessels showed somewhat thickened walls containing smooth muscle fibers (Fig. 2A). In addition to the vascular structures described above, there were remnants of papillae lined by high columnar epithelium whose interstitial stroma was replaced by numerous small, dilated blood capillaries surrounded by

Summary

A case of cavernous hemangioma of the Fallopian tube is reported, the first to appear in the literature. A brief discussion as to the pathogenesis points to the lesion herein described as a true neoplasm.

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loose fibrous connective tissue (Fig. 2B). In other places the supporting stroma of the folds were thin and relatively avascular (Fig. 3). Many of the blood vessels in the wall of the Fallopian tube were markedly dilated and filled with blood. On the basis of the above findings a diagnosis of a cavernous capillary hemangioma of the Fallopian tube was made.

The patient made an uneventful postoperative recovery and was discharged from the hospital on Nov. 2, 1937.

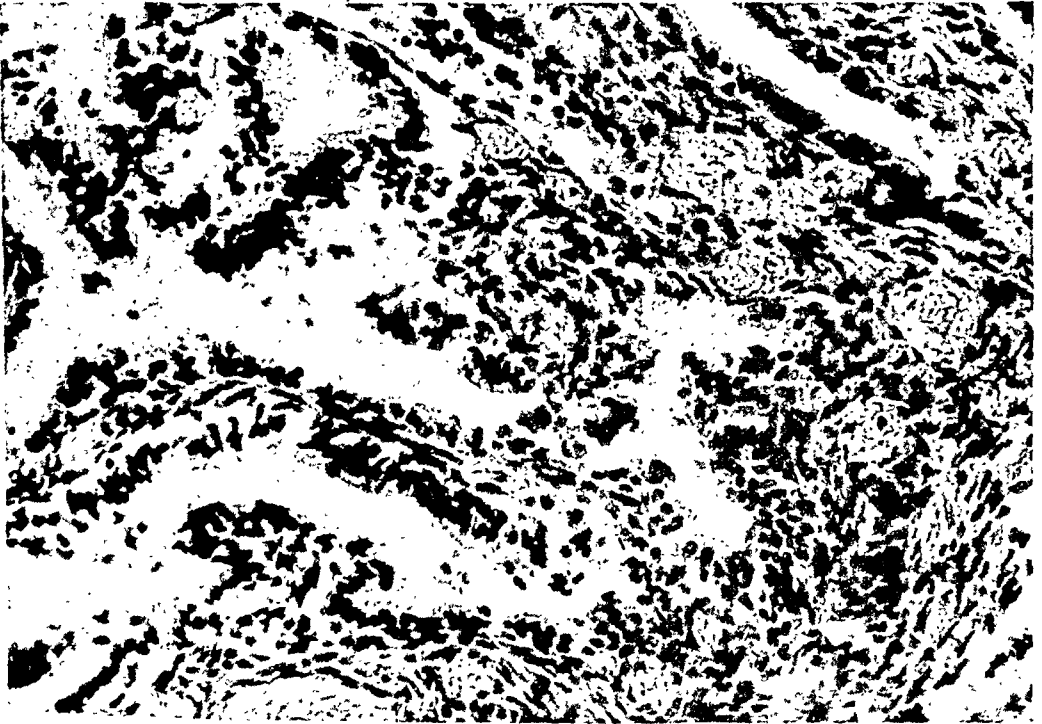


Fig. 3.—Papillary process of a Fallopian tube, lower center, showing delicate stroma supporting the columnar epithelial cells. ($\times 230$.)

Discussion

From the microscopic appearance of the tumor mass described in the Fallopian tube, it was evident to us that we were dealing with a true vascular neoplasm, particularly since many of the cavernous vessels demonstrated the presence of dense fibrous connective tissue surrounding the thin-walled, dilated blood vessels. This finding supports the view of Borst and Rindfleisch,⁵ who believe the fibrocellular growth in and about the wall of the capillaries play an important part in the development of the tumor. The retraction of this fibrocellular tissue tends to shorten the vessel resulting in dilatation on a mechanical basis.

As to other factors which may be involved in the production of dilated cavernous blood vessels, one can eliminate torsion or trauma in this case since the viability of the tissue was apparent and no extravasation of blood was noted in the folds or wall of the tube. Inflammatory changes, we feel, as characterized by the formation of vascular granulation tissue, does not play a role in the tumor reported here. In our case the folds are well preserved and the supporting stroma of the folds, in places, shows a marked angiomatous appearance of the small capillaries with no infiltration of lymphocytes or polymorphonuclear leucocytes. Where the characteristic vascular angiomatous structure is not apparent the normal stroma prevails,

X-ray of the specimen in both anteroposterior and lateral views revealed a complete vertebral column with bodies, spinous processes, and transverse processes well made out, as well as the bones of all four extremities.

On section of the mass, calcification extended inward for a distance of $\frac{1}{2}$ cm. Necrotic material was densely scattered within deposits of calcium salts. Microscopy shows no tissue which could be definitely identified histologically, and there was a dense and irregularly clumped infiltration by calcium salt deposits. The specimen was classified as a true lithopedion.



FIG. 1.—Lithopedion with lower extremity below and upper extremity above—middle shadow area, and ovoid lighter zone corresponding to head of fetus. Above is seen a folded darker mass of tissue which is sigmoid colon attached by dense fibrous adhesions.

Not all calcified masses in the pelvis are lithopedions. Another instance of a completely calcified mass in the identical location in the posterior cul-de-sac is presented for comparison. This mass measured 2 by 2 by 2 cm., and was attached by thick adhesions to the posterior uterine wall and sigmoid colon in the posterior cul-de-sac. It also presented an incidental finding at necropsy in a case of arteriosclerotic heart disease and congestive failure. A careful history served to rule out a possible lithopedion in this instance. This was confirmed by the histological picture which showed calcification of lobulated fat tissue with preservation of the reticulum structural pattern of fat tissue. The mass was completely calcified and the final decision was that it represented a calcified epiploic appendage. Several such instances have been seen in this laboratory and they undoubtedly represent secondary calcification in an epiploic appendage which has undergone infarction changes due to torsion of its pedicle.

Summary

A case of a true lithopedion which was an incidental finding at necropsy is added to the literature and brings the total to 247 instances. The lithopedion was asymptomatic and undiagnosed though present for at least thirty years.

A second instance of a calcified mass in the identical location proved to be a calcified appendage epiploica.

TRUE LITHOPEDION—INCIDENTAL FINDING AT NECROPSY AND REVIEW OF THE LITERATURE

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AS HAS already been noted, the finding of lithopedions is now rare, because of the more frequent diagnosis of extrauterine pregnancy and early surgical intervention. The incidence of 1.5 to 1.8 per cent, as quoted by Schumann, is acceptable, though he thought these figures were too high.

Reeves and Lippman,¹ in 1941, brought the grand total of reported cases to approximately 236, covering the literature of nearly five centuries. Since then ten additional cases have been added by Gigl,² Ogden,³ Wanderley,⁴ Kelkar,⁵ Doneluzzi,⁶ Tractenburg,⁷ Mayer and Berson,⁸ Biskind,⁹ Penick,¹⁰ Sant-Anna.¹¹ All of these cases meet the requirements set forth in the classification of lithopedions as proposed by Kuechenmeister.¹² All are single cases, many associated with other abnormalities of pregnancy. These ten, with the one herein reported, bring the grand total to approximately 247 cases.

Kuechenmeister¹² noted that calcification is not entirely limited to the fetus, but may involve the membranes and placenta, or be entirely limited to the placenta. On this basis he proposed the division into three groups:

1. Lithokelyphos (stone sheath or egg shell), in which the membranes alone are calcified and form a hard shell surrounding the fetus. The fetus may undergo slight change only or may be completely skeletonized, but is not involved in the process of calcification.

2. Lithokelyphopedion (stone-sheath child) in which both the membranes and the fetus are calcified.

3. True lithopedion (stone-child) in which the fetus is infiltrated with calcium salts and calcification of the membranes is negligible.

The present case meets all criteria laid down and is unusual in that it was present for at least thirty years, asymptomatic, and remained undiagnosed during life.

Case Report

A woman, aged 74 years, was admitted to the medical service of Queens General Hospital with a history of rheumatic fever at the ages of 16 and 31 years, and progressive dyspnea, orthopnea, and ankle edema. She had three grown children and recalled no episode of miscarriage, unusual menses, or bouts of severe lower abdominal pain.

The patient died four days after admission. At necropsy a completely calcified mass measuring 7 by 5 by 3 cm. (Fig. 1) was found lying free in the posterior cul-de-sac attached by thick adhesions to the superior aspect of the posterior uterine wall and sigmoid colon. There was no encroachment on either of these organs. The external surface grossly revealed four calcified extremities with detailed impregnation of distal phalanges, and the vertebral bodies could be well established.

MIGRATION OF OXYURIS VERMICULARIS TO LYMPH NODE OF ROUND LIGAMENT

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INVASION of the upper portion of the female genital tract by *Oxyuris vermicularis* is not rare. It has been found in the Fallopian tubes¹ and has been reported as the etiologic agent in a case of pyosalpingitis.² Goodale and Kirschner³ found it imbedded in the peritoneum in one case and cited six other similar cases, all of which, including their own, were in women. They felt that the worm gained entrance to the peritoneal cavity by way of the genital tract. They also cited a reported case of oxyuris ova in lymph glands contiguous to an appendix in which an adult worm was found. The present case is presented to report the finding of the adult worm and ova encapsulated in a lymph node on the round ligament. So far as we are aware, this site has not been previously noted.

The patient, a 26-year-old housewife, reported to us two months after her third delivery because of lower abdominal discomfort with sense of pressure. Examination revealed a rectocele of moderate size and an apparently enlarged uterus probably due to leiomyomata. Enlarged cervical and inguinal lymph nodes were also present. Otherwise, all physical findings were normal. The Friedman test was negative. The blood count was normal (hemoglobin 14 Gm., erythrocytes 4,500,000, and leucocytes 6,500, of which 64 per cent were neutrophils, 30 per cent lymphocytes, 2 per cent monocytes, and 4 per cent eosinophils), and the Kahn reaction of the blood was negative. Because of the short interval which had elapsed since the last delivery, the patient was advised to postpone any surgical procedure for the pelvic condition for six months. This interval would also provide an opportunity to evaluate the significance of the lymphadenopathy. Increase in the symptoms and in the size of the pelvic mass during the next month, however, necessitated earlier intervention. During this time there had been no change in the cervical and inguinal lymph nodes, and the blood count remained within normal limits. The patient therefore entered the hospital for repair of the rectocele and exploration of the pelvis.

Upon opening the abdomen the mass was found to be not an enlarged uterus but a large left ovarian cyst which proved to be a benign serous cystadenoma. The left tube and ovary and the appendix were removed. In picking up the left round ligament to fasten it over the uterus in such a manner as to cover the raw surface, a nodule, 8 mm. in diameter, was found on the round ligament not far from its uterine end for which no explanation was apparent. It was removed for microscopic study. Upon examination the nodule proved to be a lymph node within which a gravid female *Oxyuris vermicularis* and ova were encapsulated (Figs. 1 and 2). Later questioning revealed no history suggestive of infestation with the nematode, and examinations of the stool and vaginal smears were negative for it. It was felt that the pathologic lymph node was an incidental finding and probably played no part in the patient's symptoms, since both worm and ova were well encapsulated. The patient's convalescence was uneventful, and she was discharged from the hospital on the thirteenth post-operative day.

The microscopic picture of the lymph node which was removed was that of a granuloma. The granuloma was sharply circumscribed by a fibrous capsule. In the center, surrounded by leucocytes, was the cross section of the worm irregularly 500 by 600 microns. It was filled with ova and there were many ova

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lying free in the adjacent area. Surrounding the worm was a wide zone of coagulation necrosis. Between this and the capsule was a relatively narrow zone of productive fibrosis which contained many young capillaries, and was intensely infiltrated with leucocytes including many eosinophils. All sections of the specimen showed several small, discrete collections of lymphocytes lying just beneath the capsule. The appearance of these areas suggested that they were remnants of lymph node structure.

Later, the most accessible inguinal lymph node, which was on the right side, was removed for study. There were considerable fibrous thickening of the capsule and of the trabeculae, hyperplasia of the lymphoid follicle, a moderate number of eosinophiles throughout the node, and considerable thickening of the arteries and veins, but no parasites nor ova were found.

The route by which the worm reached its final resting place is open to speculation. The rich lymphatic supply to the round ligaments from the Fallopian tubes and uterus, makes it interesting to postulate a direct route from the uterus to the round ligament by way of the lymph channels, but the size of the adult worm (cross section 500 by 600 microns) would seem to make this route an impossibility. We know that worms and ova have been found in the genital tract of women and in the peritoneal cavity. This route, therefore, is not beyond the realm of possibility even though it is difficult to conceive that a worm free in the peritoneal cavity would find its way to a lymph node of the round ligament without first coming to rest at some more accessible site. The fact remains, that any indication of the manner in which the worm reached its final resting place is lacking.

Summary

The finding of *Oxyuris vermicularis*, both the adult gravid worm and ova, encapsulated in a lymph node of the round ligament, is reported. The enlarged lymph node was discovered during the course of removal of a large ovarian cyst.

I am indebted to Dr. James D. Edgar, Pathologist at Mercy Hospital, and to Dr. H. S. Sumerlin, Pathologist at the Rees-Stealy Clinic, for the pathologic studies in this case.

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Fig. 1.—Cross section of gravid female *Oxyuris vermicularis* contained in granuloma of lymph node. (Photomicrograph $\times 100$.)



Fig. 2.—Ova in cross section of *Oxyuris vermicularis* found in lymph node. (Photomicrograph $\times 400$.)

The abdomen was then closed as quickly as possible with silkworm gut, in one layer, as the patient was not standing the procedure very well. She was given two pints of plasma during the operation and received 500 c.c. of whole blood on returning to her room.

Pathologists Report.—*Gross:* The specimen consisted of an irregular lobulated mass which had been separated into two pieces, one measuring 15 cm. by 15 cm., the smaller mass, 11 cm. by 6 cm. The left ovary was matted together with the tumor mass, and the attached tube was greatly elongated over the growth. The neoplasm was covered partly by a glistening dense capsule, outer surface nodular, with numerous hemorrhagic areas on its posterior aspect. The cut surface was grayish with areas of necrosis, degeneration, and hemorrhage. A small infantile uterus and a normal right tube and ovary composed a separate specimen.

Microscopic: The bulk of the tissue consisted of rather pleomorphic medium-sized to large tumor cells with oval or round hyperchromatic nuclei and abundant acidophilic cytoplasm. The cytoplasm in some areas was elongated, and suggested muscle fiber. The larger cells were more epithelial in character. Cellular areas alternated with rarified myxomatous tissue. There was diffuse infiltration and focal collections with lymphocytes which was in favor of dysgerminoma. There was also a tendency of cells to form fasciculi. The capillaries were numerous and surrounded by tumor cells. Other areas showed extensive necrosis leaving shadow cells. In another section, there was capillary dilatation and focal hemorrhage. Here the tumor was more cellular and the cells were embryonic in type. These histologic findings were similar to those described by Meyer as being characteristic of dysgerminoma.

After the operation, there was a sudden rise of temperature to 105° F., but by the second postoperative day, it reached 102° F. She was given a course of penicillin which was continued until the temperature reached normal on the fifth postoperative day. While blood was administered immediately after the operation along with intravenous glucose. The patient voided involuntarily for several days but after a course of prostigmine, she voided without much difficulty. On the eighth day, the skin sutures were removed and her incision had healed well. She was allowed out of bed on the seven day and was discharged on the eighteenth day in an improved condition. Two weeks later, she was transferred to Bon Secours Hospital, Baltimore, where she was given a rigid course of deep x-ray therapy. The patient did not improve to any great degree and, after a steadily downhill course, expired on Nov. 7, 1946, approximately three months after her operation.

DYSGERMINOMA OF THE OVARY IN A 7-YEAR-OLD CHILD

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THE patient, a girl aged seven years, was admitted to Harford Memorial Hospital on August 12, 1946, with the complaint of fever, nausea and vomiting, and pains in the abdomen of several days' duration. The father stated that the child had felt fairly well and that he did not notice any abnormality until a few days previously. The findings on admission revealed a poorly nourished, rather pale looking female child, who breathed with considerable difficulty and whose expression was rather anxious and fixed. The abdomen was distended symmetrically and a large, somewhat nodular tumor filled the entire abdomen, from the symphysis pubis and extending to the xyphoid process. The mass was rather elastic but firm in consistency, tender in some areas and, as a whole, was quite fixed. The tumor did not shift with change of position; there were no signs of ascites or areas of fluctuation. The skin overlying the neoplasm was readily movable, and there were large dilated veins over the entire abdominal wall. The external genitals were normal for a child of her age. Rectal examination revealed that the lower pole of the tumor extended deep into the cul-de-sac, was somewhat tender, and apparently well fixed. Temperature, 101.6° F.; pulse, 128; respiration, 24; red blood cells, 2,780,000, white blood cells, 11,200; hemoglobin, 57 per cent; sugar, negative; albumin, negative. Roentgen examination showed a large mass in the anterior portion of the abdomen, displacing the colon and small intestines backward. The edge of the tumor could not be seen in the anteroposterior view, but the kidney shadow and both psoas shadows were obscured. Examination of the chest showed an elevation of both sides of the diaphragm; the lung fields were clear. Intravenous pyelogram showed very little secretion in the left kidney. Right kidney showed a marked dilatation of the kidney pelvis and ureter. One large blunted calyx was shown on the left side, probably in the lower pole. Examination seemed to indicate that the mass was connected with the genital or urinary tract rather than an enlarged spleen.

At operation, there was found a solid tumor which extended from the pelvis almost to the xyphoid process. The incision was enlarged superiorly and the tumor freed by sharp and blunt dissection with considerable difficulty from the posterior abdominal wall, the lateral walls of the pelvis, and posterior cul-de-sac. It was lobulated in appearance, conformed to the shape of the pelvis and the abdomen, forming a mass roughly the shape of a watermelon. Posteriorly, the pelvic walls had been bared by the dissection and one could see the ureters, pelvic vessels and the abdominal aorta which had been exposed. The tumor could be seen arising from the left ovary. It was rather rubbery in consistency, grayish in appearance and there were numerous hemorrhagic areas over the entire posterior surface. A small portion of the anterior aspect was covered by a thick glistening capsule. The mass was solid throughout with no evidence of cystic degeneration and was apparently sarcomatous in nature. A supravaginal hysterectomy, bilateral salpingo-oophorectomy was done by the customary technique; the stump of the cervix being suspended by the round and broad ligaments and the combined stumps then being completely peritonealized by the reflection of the uterovesical peritoneum. All bleeding points were carefully ligated; several grams of sulfanilamide sifted into the pelvic cavity and the posterior peritoneum closed by a continuous No. 1 plain catgut suture.

Department of Reviews and Abstracts

Selected Abstracts

Pregnancy

Glass, S. J.: *The Importance of the Liver in Reproductive Physiology*, West. J. Surg. 55: 114, 1947.

The liver plays a dominant role in the inactivation of the estrogens. The work of Talbot is quoted which showed that in female rats in whom the liver had been partially damaged with carbon tetrachloride the uterine weights increased almost 100 per cent. When the rats were castrated, no such change was observed. It is concluded that the damaged liver, unable to inactivate the endogenous estrogen, a high estrogen level results. The author has reported the presence of gynecomastic and testicular atrophy. In males suffering with cirrhosis of the liver, free estrogen may be recovered in the urine. Impairment of spermatogenesis probably resulting from accumulated estrogen has been observed in hepatitis as well as cirrhosis. Such estrogen tends to suppress gonadal function in both male and female. Appreciation of this liver-gonadal relationship may open new therapeutic vistas in endocrinology.

WILLIAM BICKERS.

Hellman, L. M.: *The Effect of Aging on the Course and Outcome of Pregnancy*, J. Gerontology 1: 418, 1946.

The author discusses the effect of the age of the mother in the maternal and infant well-being in both primiparous and multiparous women aged 35 to 45 years. The hazards to pregnancy which undoubtedly increase in this age group should serve as warning posts that additional care must be taken when the mother is over 35 years. The author states that many radical procedures have been advocated to bring about a successful termination of pregnancy but he also thinks that these procedures must be carefully evaluated before they can be executed. In addition to the medical complications of middle age such as heart and kidney disease and diabetes, the risks to the mother include the pregnancy complications of toxemias and myomas. He states that it has been the policy of the Johns Hopkins clinic and probably the teaching clinics throughout the country to allow these older patients to deliver normally from below if the antenatal course, pelvis, presentation, birth canal, and labor are all normal. He also states that it has not been the experience there that the labors of older primiparous women are prolonged or more difficult than those of their younger sisters. However, in the age group 35 to 39 years, abdominal delivery was resorted to in 16 per cent of cases while in the 40- to 45-year age group, section was performed in 44 per cent of these cases. It would seem that the difficulties would be somewhat lessened in the case of the multiparas in the older age group but the author feels that this is not the case. The basis of maternal risk is again heart and kidney disease and diabetes while the immediate pregnancy complications are toxemia, myomas, together with increased incidence of premature separation of the placenta and spontaneous rupture of the uterus. The maternal mortality in the age group 40 to 45 years, comprising 330 deliveries, increased to 1.8 per cent. The factors of malpresentation and premature separation increased in the 35- to 45-year age group and contributed not only to the maternal but also to the fetal death rate. Age not only has a deleterious effect upon the mother but also upon the rate of fetal wastage and formation. The author states that an analysis of 16,312 deliveries occurring at the Johns Hopkins Hospital during the last decade showed the stillbirths and neonatal mortality rate was 72.8 per thousand viable births in the 206 patients over 35 years. This represents a definite increase

Editorial

The Third American Congress on Obstetrics and Gynecology

The Third American Congress on Obstetrics and Gynecology was held in the Municipal Auditorium, St. Louis, Mo., Sept. 8 to 12, 1947, and was highly successful from all aspects.

There were more than 1,500 advance, and 500 paid registrations at the Congress. Actually in attendance were 1,307 of these 2,000 paid registrants, and over 1,000 additional people, a total of more than 2,300. The bulk of those attending were physicians and nurses, but there was a generous admixture of others with interests touching the combined specialty. This was the largest attendance of the three American Congresses, including many Canadian, Mexican, and South American colleagues. They were most welcome, and a cordial invitation is extended to them to participate in future American Congresses, especially the next, which is to be jointly an International, and the Fourth American Congress.

The scientific sessions were well attended. Mornings were devoted to general meetings, in the form of panel discussions, at which the nation's outstanding authorities discussed "Anesthesia and Analgesia," "Cancer of the Cervix," and "Cesarean Section." Each afternoon from 2:00 P.M. to 3:45 P.M. there were two, and sometimes three section meetings. From 4:00 P.M. to 5:00 P.M. at least five round tables were held daily, and were so popular seats were at a premium.

The American Society for the Study of Sterility, and the National Federation of Obstetric and Gynecologic Societies each was responsible for a segment of the program, a plan truly embodying the fundamental idea of a "congress."

More than sixty manikin demonstrations were given. These were acclaimed at the Second, and well received at the Third Congress. The motion picture program was almost too full, since each film was shown but twice, despite the fact the theater was in continuous operation each day.

Thirty scientific exhibits offered a wide variety of subject material. The prize was awarded to Doctors Flexner, Vosburgh, and Cowie of Baltimore, who presented "Sources of Fetal Iron and the Permeability of the Placenta to Iron as Demonstrated with Radioactive Iron."

Ninety-seven booths were occupied by technical exhibitors, demonstrating every variety of drug, instrument, and service in the field of obstetrics and gynecology.

The scientific papers presented at the various sessions, together with the accompanying discussions, will be published in a special volume of *Transactions* at a later date.

The success of the Third American Congress on Obstetrics and Gynecology was outstanding, and it was decided to expand it to international proportions in 1950. Further announcements will appear in subsequent issues of the JOURNAL.

actions following blood transfusion and drugs. In the group of accidental deaths, the author includes pulmonary embolus, pulmonary atelectasis, air embolism, acute dilation of the stomach, rupture of a large extragenital vessel, or aneurysm and congestive heart failure.

For treatment the author recommends (1) continuous oxygen as cell anoxia increases the shock, (2) blood plasma in much greater quantities than is generally used in hemoconcentration and whole blood where hemodilution is present, and (3) adrenal cortex as a regulator of capillary tension.

WILLIAM BERMAN.

Friedman, Louis L., and Garber, J. R.: *Pregnancy and Tuberculosis; the Present Status of the Problem*, Am. Rev. Tuberc. 54: 275, 1947.

A review of the literature is presented on the effect of pregnancy on tuberculosis. This shows that it is now generally accepted that pregnancy has little or no influence on the incidence or course of tuberculosis. Therapeutic abortion is rarely indicated because of tuberculosis; and should never be attempted after the first trimester of pregnancy. Tuberculosis must be treated in the pregnant woman as in the nonpregnant; if pneumothorax is indicated it should be carried out during pregnancy. Even bilateral pneumothorax may be employed if the disease is bilateral. One of the authors (L. L. F.) has had two patients in whom bilateral pneumothorax was done during pregnancy, who were safely delivered of normal living children. The best results are obtained if tuberculosis is discovered and treated actively before pregnancy occurs. The early recognition of tuberculosis in women of childbearing age will be aided by the various methods of mass x-ray examination of the chest; their use in prenatal clinics is also advised.

If the tuberculosis is discovered and treated before the patient becomes pregnant, many authorities believe that pregnancy should not be advised until one to three years after the disease has been arrested.

When a tuberculous patient is pregnant arrangements should be made well in advance for hospitalization of the patient for delivery, if possible in a tuberculosis sanatorium that is equipped for special care for mother and child. When delivery is from below, episiotomy and/or low forceps should be employed to shorten the second stage of labor. Cesarean section may be done; some obstetricians consider cesarean section the method of choice for delivery of tuberculous mothers, but the authors are of the opinion that it is the procedure of choice only when there is some obstetric indication for operative delivery, or if sterilization of the patient has been agreed upon.

It has been found that 81 per cent of the children of tuberculous mothers are delivered alive, and that most of these children are normal in every respect. But special precautions must be taken at the time of delivery, and mother and child must be separated immediately to avoid infection.

HARVEY B. MATTHEWS.

Hamilton, Burton E.: *Heart Disease in Pregnancy*, Missouri M. A. 44: 17, 1947.

At the Boston Lying-In Hospital, 17 of every 1,000 women have rheumatic heart disease; these women have contributed to the maternal deaths 140 out of every 1,000 deaths. It is thus evident that pregnancy in a woman with heart disease constitutes a real problem to the obstetrician.

Regular examinations of a woman with cardiac disease should be made after marriage, as the cardiac status may change at any time. Even the fact that a woman has survived one pregnancy does not ensure her safety in the next pregnancy. Pregnancy is safer for women who are able to live reasonably normal lives without showing cardiac symptoms and have no complication than in those who show signs of heart failure while normally active and who have some complication, especially hypertension. The maternal death rate in the latter group is 16 per cent. In patients with auricular fibrillation, the outlook is still more unfavorable, the maternal death rate being nearly 33 per cent. Recurrences of rheumatic fever in patients with chronic rheumatic heart disease are rare in pregnancy; but most of such recurrences occur in young women under 23 years of age. In women over 35 years of age

from the rate of 57.7 quoted previously for all *prima gravida* patients regardless of age. There is an additional factor which was discussed by the author. He states that there is a diminution of the reproductive vigor as maternal age advances and the incidence of fetal abnormalities and certain congenital diseases such as mongolism and achondroplasia increases. He quotes the classic studies of Eleyer which seem to show that there is a tendency for mongoloid infants to be born to older mothers averaging 41 years. In view of all these factors, the author states that the greatest talisman of the young married woman is youth and that the formation of her family should not be too long delayed.

The hazards of pregnancy, both to mother and child, increase with the age of the mother. Maternal and infant mortality rates increase, both in *primiparous* and *multiparous* women. The medical complications of middle age, such as heart and kidney disease, hypertension, and diabetes, and such complications of pregnancy as toxemia, myomas, and malpresentation increase with the age of the mother and the number of children she has previously borne. In addition, there is a higher incidence of fetal abnormalities and certain congenital diseases from the age of 30 years onward. Since 14 per cent of all births occur to mothers 35 years of age and above, these hazards of pregnancy are most important and should be carefully watched.

EDWARD C. HUGHES.

Crew, F. A. E.: *Twins and Triplets, Quadruplets and Quintuplets; Some Facts and Fallacies*, Practitioner 158: 233, 1947.

Twins may be monovular or binovular; if monovular, developing from a single ovum fertilized by a single spermatozoon, the twins are genetically the same and of the same sex. Binovular twins may be of different sex and may differ genetically as any two siblings. The same statements apply to monovular and polyovular multiples. It must be remembered, however, that monovular and polyovular multiples cannot always be distinguished by differences in their embryonic membranes. Monovulars usually have a single chorion, but if the division into separate embryos has occurred relatively late they may be polychorionic. Similarly polyovulars are usually polychorionic, but fusion of the original separate membranes may have occurred so that they seem to be single.

While it has been suggested that a greater frequency of multiple births might be an aid in maintaining the growth of the population, the author points out that premature births, stillbirth, and birth injuries occur much more frequently in multiple births; neonatal mortality is also higher.

The study of twins, or of triplets, quadruplets, and quintuplets is of special interest in regard to determining the relative importance of heredity and environment, especially in the cases of monovulars. Monovulars are genetically identical, and any differences that they present must be the result of environmental factors; such environmental factors may be intrauterine or extrauterine. There are a few characteristics that are determined by hereditary forces, such as blood group, eye color, and sex, but most characteristics are the product of the interaction of heredity and environment. Comparative studies of monovular and polyovular multiples would also be of value in determining the relative importance of etiologic factors in disease—the predisposition of the individual and the immediate provocative cause in the environment. Because of this, special attention should be given to multiples, as scientific methods of prevention and treatment of disease depend upon accurate knowledge of etiology.

HARVEY B. MATTHEWS.

Pregnancy, Complications

Johnson, Herman W.: *Sudden Death in Obstetrics*, Arizona Med. 3: 225, 1946.

When sudden death occurs in the obstetric patient the causes may be reduced to residuum of (1) obstetric shock, (2) hemorrhage, and (3) combination of shock and hemorrhage. Accidental shock as the cause of sudden death in the obstetric patient comprises the largest group. Shock appears most frequently in cases of (a) pre-eclampsia and eclampsia, (b) dystocia from any cause followed by exhaustion, dehydration, blood loss, and (c) anaphylactoid re-

after the suppositories were inserted by the slide-cell technique. Significant levels of penicillin were found in the blood after one, two, or three suppositories, the levels being somewhat higher after vaginal than after rectal suppositories. Vaginal penicillin suppositories were used in a small group of ambulatory patients with acute vaginitis; this resulted in rapid symptomatic improvement and local healing. The results of these studies indicate that penicillin suppositories might be used as a routine measure in preparing patients for delivery, especially when premature rupture of the membrane has occurred. Penicillin suppositories might also be used in preparing patients for cesarean section and for vaginal or abdominal hysterectomy.

HARVEY B. MATTHEWS.

Radiation

Haman, John O.: X-Ray Irradiation to Promote Ovulation, *West. J. Surg.* 55: 107, 1947.

X-ray irradiation to pituitary and ovaries for the treatment of amenorrhea is again recommended. The observation that fetal abnormalities in certain animals may occur in the second or last generation following irradiation has militated against its use in the human. The author believes that its danger has been exaggerated. The basal temperature curve has been used as a basis for determining the ovulation salvage following treatment. The technic employed has varied, but in each case the pituitary and ovaries were radiated. The number of treatments was three.

Eighteen patients were treated and of this group 12 whose chief complaint was sterility and amenorrhea became pregnant. The offspring were normal in all the patients who carried to term. Restoration of normal menstrual function as shown by basal temperature and biopsy was obtained in 71 per cent of 32 cases with secondary amenorrhea.

In a discussion of this report Dr. Rubin confirmed from his own experience the observations here recorded and states that low dosage, irradiation of the pituitary and ovaries in amenorrheic, sterile women is today the most satisfactory method of treatment.

WILLIAM BICKERS.

Venereal Diseases

Olansky, Sidney, and Beck, Robert: Rapid Treatment of Prenatal Syphilis, *Am. J. Syph. Gonorr. & Ven. Dis.* 31: 51, 1947.

The authors give the following conclusions on this article:

1. Intensive treatment of prenatal syphilis offers the best outlook for the prevention of congenital syphilis. It is essential that quantitative serologic tests for syphilis and careful physical examinations be performed monthly during pregnancy so that in the event of infection, reinfection, or relapse, re-treatment may be instituted in time to prevent congenital syphilis.

2. Intensive antisyphilitic treatment even late in pregnancy results in a very high incidence of nonsyphilitic infants.

3. The cord serologic test for syphilis appears to be of little value in a diagnosis of congenital syphilis.

4. The incidence of untoward reactions in all three regimes here employed was very low, particularly with the schedules employing penicillin alone and penicillin, arsenic, and bismuth in combination.

C. O. MALAND.

Porter, J. R.: The Positive Serological Reaction Is Not a Diagnosis of Syphilis, *Illinois M. J.* 71: Feb., 1947.

A plea is made for wider recognition of the prevalence of false positive serologic tests for syphilis. The author points to the nonspecificity of these tests and the variety of disorders of serum protein which will give positive reactions. He therefore urges that a diagnosis of syphilis should rest on clinical as well as laboratory data, and that treatment should be withheld until such definite clinical evidence is forthcoming in any given patient. S. B. GUSBERG.

there are twice as many instances of congestive heart failure during pregnancy as in younger women. The safest age period for pregnancy in cardiac patients is, therefore, between 23 and 35 years of age. Involvement of the mitral valve alone is more favorable than involvement of the aortic valve alone. The most favorable cases are those in which there is only moderate enlargement of the heart and a loud apical systolic murmur.

A study of the time of occurrence of heart failure in pregnancy in cardiac patients and of the circulatory changes in normal pregnancy shows that failure does not occur in uncomplicated cardiac cases before the sixth month of pregnancy; it is most frequent in the seventh and eighth months; and rare in the ninth month; and that the circulatory load of pregnancy begins to become heavy in the sixth month, increases in the seventh and eighth months, and decreases again in the ninth month. Therefore delivery before term is not indicated in cardiac patients, as the circulatory load is decreased near term.

Throughout pregnancy the cardiac patient must be under careful supervision and on a carefully planned regime which must be followed exactly. If the patient shows signs of embarrassment of the circulation and respiration, her activity must be still further restricted. If symptoms of congestive heart failure develop, she must be kept in bed under hospital conditions. Both sodium intake and fluid intake should be restricted in cardiac patients during pregnancy. With such a regime the maternal mortality of cardiac patients can be reduced, and, in the author's experience, has been reduced.

Studies of hypertension in pregnant women have indicated that women with hypertension are no better off than women with rheumatic heart disease in relation to the risk of pregnancy. Much more study of hypertension in pregnancy and of the effect of pregnancy on hypertension is necessary.

HARVEY B. MATTHEWS.

Puerperium

Perabo, Franz: Investigations Upon the Shift of the White Blood Cell Count and the Sedimentation Rate in the Afebrile Puerperium, *Gynaecologia* 122: 15-62, 1946.

Perabo, at the University of Zurich Woman's Clinic, conducted unusually detailed investigations on the hemoglobin, the total white blood cell counts, differential white blood cell count and the hematocrit determinations upon nearly 200 afebrile puerperal cases. Nearly all the cases were examined in the delivery room with decreasing numbers upon the fifth, ninth, twenty-first, and forty-second postpartum day; 217 cases at the time of delivery, 195 cases upon the fifth and ninth days; 45 cases, the twenty-first days, and 26 to 30 cases upon the forty-second day.

Using 200 cells for each count, modified Giemsa stain and biostatistical methods, the author observed that the leucocyte count was slightly raised (12,100 with a mean deviation of 3,000) during labor, became approximately normal on the fifth day (7,900 with a mean deviation of 1,800) and absolutely normal on the ninth day postpartum (6,900). Perabo states an increase of leucocytes in the puerperium of more than 1,000 above the 6,900 figure must be due to a special cause and not ascribed to the puerperium itself.

The sedimentation rate accelerated up to 50 mm. during labor showed a gradual decrease in rate although still remaining slightly increased over the average nonpuerperal figure at the end of the sixth week. The author was unable to demonstrate any significant correlations of the hemoglobin on the sedimentation rate. The article is well illustrated with tables and charts.

C. E. FOLSOME.

Lovelady, Sam B., Randall, Lawrence M., and Hosfeld, S. Marjorie: Levels of Penicillin in the Blood After the Use in the Vagina and Rectum of Suppositories Containing Penicillin Calcium; Preliminary Report, *Proc. Staff Meet., Mayo Clin.* 21: 401, 1946.

In the first part of the study suppositories containing 100 units of penicillin calcium were placed in the rectum or vagina of postpartum patients without complications, while they were confined to bed. In 36 cases the suppository was placed in the vagina, and in 33 cases in the rectum. The level of penicillin in the blood was determined three and five hours

Correspondence

Some Comments on Hysterosalpingography

To the Editor:

In the June, 1947, issue of the JOURNAL, Dr. Paul Titus wrote on "Oil Embolism From Hysterosalpingography." He emphasized three distinct points and these are repeated below.

First, Dr. Titus said that "altogether too many hysterosalpingographies are being performed." He restricts the use of hysterosalpingography to only those cases where the desired information cannot be obtained by the Rubin test.

Second, he maintained that "iodized oil should not be used as the opaque medium because it is a foreign body remaining as such wherever it is injected. It is not absorbed and eliminated, but remains encysted within the pelvis when passed through the tubes, or becomes a highly dangerous embolic agent if accidentally injected into a vein." Titus advocates the use of an aqueous Skiodan-acacia mixture whenever hysterosalpingography is to be resorted to.

Finally, he stresses the importance of proper technique in hysterosalpingography in order to preclude hazards from this procedure.

Dr. Titus' remarks have evoked the following comment. With his first two points I take qualified exception, and with his third point I am in wholehearted accord.

Contrary to Dr. Titus' opinion, I have found that far too few hysterosalpingographies are being performed today, even though they are indicated. True, too many are being improperly and carelessly performed, but certainly a technique should not be condemned when the fault lies with the operator. One would not junk the automobile because there are far too many drivers who handle cars recklessly. It should be our purpose, rather, to insist that definite precautionary and safety measures be employed. As a matter of fact, the judicious use of hysterosalpingography in the hands of trained technicians is rapidly becoming one of the most important implements in the diagnosis and treatment of female sterility. Illustrative of this point, Rutherford¹ has recently shown the value of *repeated* iodized oil instillations in women who were unable to become pregnant.

I also am not unaware that some iodized oil preparations (notably those used abroad from where most of the embolic phenomena have appeared in the literature) may act as foreign bodies and may be slowly, if ever, absorbed. However, there is an iodized oil available* manufactured and sold by an American concern, which is absorbable when used in physiologic amounts. From my experience it is obvious that the peritoneum can absorb the small amount of intra-abdominal iodized oil required for use in hysterosalpingography. In 87 successful pregnancies following the iodized oil technique, follow-up x-rays were obtained at about the fifth month of gestation or as soon as fetal parts were discernible. Owing to the fact that not more than 4 to 5 c.c. of iodized oil had been used for each hysterosalpingography, no evidence of the opaque substance could be found in the peritoneal cavities of 82 of the patients. In four of the cases, the opaque substance was barely visible; while in only one patient was definite evidence of unabsorbed oil found. No symptoms were referable to the oil and the pregnancies progressed without mishap.

It would seem, from the recent scientific exhibit of Brown, Bradbury, and Jennings² held at the A. M. A. Centennial in Atlantic City, that Dr. Titus' beliefs concerning the absorption of iodized oil were confirmed. However, when Dr. Irving F. Stein of Chicago and I discussed the x-ray plates with Dr. Jennings at the booth, she readily admitted that greater quantities of iodized oil had been instilled intraperitoneally than were necessary for actual testing. The point I stress is, that where 4 to 5 c.c. of iodized oil are used rather than 9 to 10 c.c. there exists little or no problem of oil absorption.

*G. D. Searle and Co. of Chicago manufactures Iodochlorol, a satisfactory iodized and chlorinated peanut oil combination.

Guerriero, Wm. F., and Mantooth, W. B.: Syphilis of the Cervix, South. M. J. 40: 261, 1947.

The cervix is a common portal of entry for the *Spirocheta pallida*. The chancre of the cervix, due to its environment, loses very early in its development the characteristic induration and rolled edges, its appearance soon becoming indistinguishable from a simple erosion. Secondary lesions of syphilis are gray-white in color which may resemble other benign cervical lesions. Repeated dark field examination is necessary for differential diagnosis.

WILLIAM BICKERS.

Anatomy

Zambonini, Annibale: Abnormalities of the Umbilical Cord, *Rivista Italiana di Ginecologia* 28: 60-75, 1945.

In a series of 10,295 placentas which were studied at the Medical College of Bologna by Zambonini in regard to abnormalities of the umbilical cord, phenomena of the cord of varied categories were found. A wide variation in the length of the cord was noted. The length of the cord averaged 50 cm., the shortest cord measuring 20 cm., twelve cords being longer than 100 cm., the largest reaching the extreme length of 170 centimeters.

None of the very rare phenomena such as hematomas, real tumors, true or false cysts were found in this survey. Twisting of the funis was frequently present, in no case, however, the coiling being such as to endanger the fetal life. True and false knots also frequently occurred, but again neither of them involved serious conditions.

Velamentous insertion of the funis was present in 48 cases (0.46 per cent), and eventuated two cases of fetal death in prematurely born twins.

Absolute shortness of the cord (less than 30 cm.) was present in 45 cases (0.43 per cent), and of these, 36 did not exert deleterious influence on the course of delivery; death occurred, however, in two cases in which the cord measured 20 cm. and 25 cm., respectively, a length not compatible with normal delivery.

Excessively long cords were largely represented; no deleterious consequences, however, were noted, except in cases in which the abnormal length was associated with loops, the cord being wrapped around portions of the fetus.

Loops were present in 1,185 of the cases, in 1,166 cases the child's neck being encircled, in 19 cases the loop of the cord wrapped around different portions of the fetal body. In eleven cases, fetal death occurred, which corresponds to a mortality rate of less than 1 per cent. Presentation of the cord occurred in only seven cases with no complications.

Prolapse of the funis occurred in 43 cases, and resulted in death of the fetus in 19 cases: i.e., in 44 per cent of the cases, which is not too high a percentage for this serious complication.

True knots were found in 57 cases, in six cases of which they were fatal to the fetus. The deleterious influence of the abnormalities of the cord in this quite comprehensive series is lower than usually quoted.

GEMMA BARZILAI.

Abortions

Russell, P. B., Jr.: Abortions Treated Conservatively, South. M. J. 4: 314, 1947.

A plea is made for the conservative management of abortions. Conservative treatment failed only thirty-five times in a total of 2,406 cases of incomplete abortions. A comparison is made between the uterus recently aborted and the uterus following full-term delivery. The placenta during the early months of pregnancy is less firmly adherent to the uterus and, therefore, more readily expelled once the cervix is dilated. Dilatation and curettage with packing was done in only 5.2 per cent of patients with abortions, spontaneous and criminally induced and at various stages of gestation. Uncontrolled hemorrhage was the chief indication for surgical interference. Conservative treatment consisted of the usual supportive treatment and 1 c.c. doses of pituitrin as required for bleeding. In those cases where operation was performed, only the sponge stick was used. Control of infection was the greatest problem, but during recent years penicillin and streptomycin have strengthened the therapeutic hand.

WILLIAM BICKERS.

Item

American Board of Obstetrics and Gynecology, Inc.

Examinations

The next written examination (Part I) for all candidates will be held in various cities of the United States and Canada on Friday, Feb. 6, 1948, at 2:00 P.M. Candidates who successfully complete the Part I examination proceed automatically to the Part II examination held later in the year.

A number of changes in Board regulations and requirements were put into effect at the last annual meeting of the Board held in Pittsburgh, Pa., from June 1 to June 7, 1947. Among these is the new ruling that the Board does not subscribe to any hospital or medical school rule that certification is to be required for medical appointments in ranks lower than Chief or Senior Staff of hospitals, or Associate Professorship in Schools of Medicine, for the obvious reason that such appointments constitute desirable specialist training. At this meeting the Board also ruled that credit for graduate courses in the basic sciences which involve laboratory and didactic teaching rather than clinical experience or opportunities will be given credit for the time spent up to a maximum period of not more than six months, regardless of the duration of the course.

Applications are now being received for the 1948 examinations. Closing date for these applications will be Nov. 1, 1947.

For further information and application blanks address Paul Titus, M.D., Secretary, 1015 Highland Building, Pittsburgh 6, Pa.

PAUL TITUS, M.D.

Dr. Titus also pointed out that every once in a while a patient is encountered sensitive to iodized oil, and will react to it. Certainly, those who have used Skiodan extensively realize that this preparation is also not without its allergic and untoward reactions.

Finally, I am in complete agreement with Dr. Titus in stressing the importance of proper technique in hysterosalpingography. Any physician who blindly disregards precautionary measures and haphazardly shoots 10 c.c. of a foreign substance into anybody's peritoneal cavity should be called to task. Far too many tests are being performed with a 10 c.c. syringe filled with a foreign substance, the syringe emptied into the uterus without regard to manometric pressure or force. Far too many are being performed too close to the time of the menstrual period. Far too many are being performed too soon after a curettage or endometrial biopsy. Far too many are using cannula tips that are crushing and damaging to the tissues of the cervix and uterus.

There is no excuse today for the physician who does not employ every available safeguard in the performance of hysterosalpingography. It was with this in mind that Beclere³ and Jarcho,⁴ twenty or more years ago, each perfected a manometric instrument and suggested a fluoroscopic technique in the performance of uterotubal x-rays. It was what I had in mind when I took the best features of Beclere's Hysterometer and Jarcho's Pressometer and then conceived the Gynograph⁵ which allowed me to perform 1,400 consecutive hysterosalpingographies with iodized oil without a single instance of venous intravasation or embolism.

If the physician performing hysterosalpingography will but make use of every precautionary measure in this intra-abdominal technique, cases of pulmonary embolism like the one reported by Ingersoll and Robbins,⁶ in which these authors acknowledged that their procedure was "ill-advised," can be eliminated.

Again I reiterate, let us not condemn a procedure, which like exposure to gamma rays can do much good, but which when used wrongly can wreak havoc with human life.

ABNER I. WEISMAN, M.D.

1160 FIFTH AVENUE
NEW YORK, N. Y.
July 12, 1947.

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Reply by Dr. Titus

To the Editor:

Notwithstanding Dr. Weisman's comments, I have no changes to make in my original statement. This was, in effect, that uterotubal insufflation with gas or air (Rubin test) is safe as well as diagnostically sufficient in the majority of cases; that injection of certain radiopaque substances for hysterosalpingography is relatively dangerous, with reported fatalities; that this should not be made an unnecessary substitute for uterotubal insufflation, as many, including Dr. Weisman, seem to suggest; and that when such injections are made, upon proper indications, proper technique should be used to avoid accidents.

PAUL TITUS, M.D.

PITTSBURGH, PA.
August 15, 1947

cinoma of the uterus; this would seem to deprive workers in this field of a proper genetic substrate upon which to attempt the provocation of abnormal response by growth-stimulators. Yet much significant work has been done.

Overholser and Allen^{4, 15} produced atypical growth in the cervix of monkeys by combining prolonged injection of estrogens with trauma to the cervical epithelium. This abnormal growth response was certainly a form of hyperplasia rather than carcinoma, but it did resemble certain borderline cervical lesions which we are now learning to recognize in the human being. Engle and Smith¹⁶ and Zuckerman¹⁷ also reported failure to obtain uterine carcinoma in monkeys by long-term estrogenic stimulation. In the years 1934 to 1939, a variety of atypical growths were reported following estrogen injection, but certainly few of these could be definitely classified as cancer, and still fewer significantly related to spontaneous human tumors¹⁸⁻²⁴. Lacassagne¹⁹ described rather active squamous metaplasia in the uterus of a mouse treated with estrone. This tissue contained numerous mitotic figures and invasion of the submucosa at one point, but no metastases. Perry and Ginzton²³ reported the production of uterine carcinoma in a few mice of a group which had received both theelin and 1:2:5:6 dibenzanthracene.

The studies of Allen, Gardner, and their co-workers were finally fruitful in producing true carcinoma of the cervix in mice by prolonged estrogen stimulation.²⁵⁻²⁸ In 1938 they reported eighteen invasive cervical tumors produced in mice; these tumors metastasized to lymph nodes and could be transplanted to several generations of hosts. In 1941 and 1942 they reported significant numbers of cervical carcinomas produced in hybrid mice by chronic estrogen therapy. Miller and Pybus²⁹ reported similar results in 1942.

Thus a notable accomplishment had been attained: the production of malignant uterine neoplasms with estrogens in rodents, ordinarily resistant to the spontaneous growth of such tumors.

The reports of Burrows³⁰ and Greene³¹ concerning spontaneous adenocarcinoma of the endometrium in rabbits must also be regarded as significant. Both these workers encountered evidence elsewhere in the body suggesting an endocrinopathy in these tumor-bearing animals. Greene described preceding toxemia and liver damage with a period of infertility and "cystic endometritis" leading up to tumor formation and he interpreted these findings as evidence of abnormality in the pattern of internal secretions. Naturally in speculation about abnormal growth patterns in these animals one is attracted to implication of the estrogens.

Since species differences evidently are of considerable significance in the study of abnormal growth of the endometrium, evidence of an endocrine-tumor relationship in the human being is important. We have studied this problem clinically and histologically in respect to abnormal endometrial growth, and wish to present data in the following categories: (a) the stimulating effects of functioning ovarian tumors; (b) hyperplasia of the human endometrium following prolonged estrogen administration; (c) adenocarcinoma of the human endometrium following prolonged estrogen stimulation; (d) relation of hyperplasia of the endometrium to the development of adenocarcinoma.

(A) *Response of the Human Endometrium to Granulosa Cell Tumor of the Ovary.*—A natural, if uncontrolled, experiment in prolonged estrogen stimula-

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PRECURSORS OF CORPUS CARCINOMA ESTROGENS AND ADENOMATOUS HYPERPLASIA

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STUDY of growth-stimulating substances in relation to the female reproductive tract leads one shortly to a consideration of the role of estrogens in carcinogenesis in these organs. The intense stimulating effect of estrogenic substances on growth of the endometrium is well known, and one can readily understand the logic of investigators who have sought an explanation for abnormal uterine growth in this group of endocrine substances. With the acquisition of knowledge of substances which demonstrated both estrogenic and carcinogenic activity in experimental animals,¹ a fresh impetus entered these investigations. Since that time a great body of knowledge has accumulated concerning the endocrine-tumor relationship. The uterine implications of this work have been ably reviewed at various stages of its development by workers intimately connected with this field: Loeb, 1935;² Taylor, 1938;³ Allen, 1938;⁴ Gardner, 1939;⁵ Loeb, 1940;⁶ Allen, 1940;⁷ Greene and Brewer, 1941;⁸ Allen, 1942;^{9, 10} Taylor, 1944;¹¹ Nathanson, 1944;¹² and Burrows, 1945.¹³

Study of the evidence for carcinogenic activity of estrogenic substances in experimental animals underscores the importance of species differences and the genetic factor. However, knowledge of this importance of a genetic factor in no manner vitiates the significance of the growth-stimulating activity of estrogens in these animals, and it is a fact that carcinoma of the cervix has been produced in mice by prolonged injection of estrogens. It is an interesting fact that a properly susceptible tissue is needed for this abnormal growth response, but if one accepts the broader concept of the term carcinogenesis, one cannot deny such an activity to the estrogens in certain laboratory animals.

It is perhaps unfortunate for such investigations that the commonly used laboratory animals—rodents and monkeys—rarely develop spontaneous car-

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developed cystic glandular hyperplasia, but others show greater activity, with papillary buds in the glands, extreme crowding of glands, heaping up of the epithelium, and sometimes more eosinophilic staining—all qualities which we have noted in endometria stimulated by exogenous estrogens. One can place these hyperplastic endometria in a graded progression of activity which moves quite readily toward the malignant one (Figs. 1 to 7).

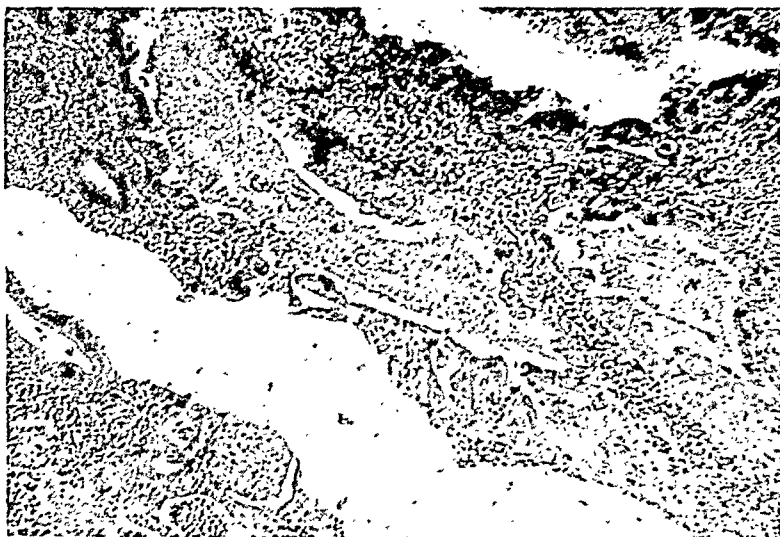


Fig. 2.—($\times 240$) Pale staining glands with mildly papillary pattern.

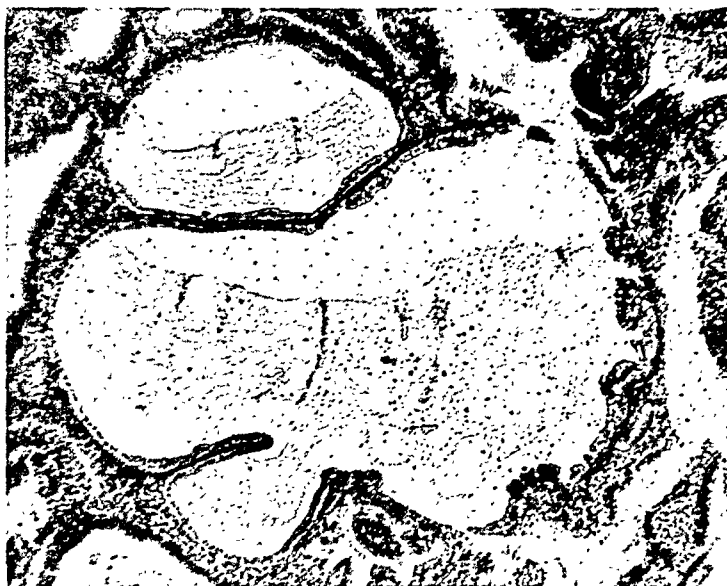


Fig. 3.—($\times 210$) Intraglandular budding scattered through endometrium which otherwise shows ordinary hyperplastic pattern.

This accumulating evidence of the association of estrogen-producing ovarian tumors with corpus carcinoma together with data obtained from study of the pattern of adenomatous hyperplasia produced in such cases are certainly suggestive of an estrogen-cancer relationship.

tion of the post menopausal human uterus is set up in the patient who develops a granulosa cell (or theca cell) tumor of the ovary: these patients are frequently advanced in years, the estrogen stimulation is prolonged, and it lacks rhythmicity or interruption, for there is no regular corpus luteum formation to modify the constant estrogenic effect. The finding of hyperplasia of the endometrium in patients harboring such an ovarian tumor is well known. If prolonged unopposed estrogen stimulation can produce endometrial carcinoma in individuals of such an age group,³² one would expect a significant percentage of those patients—if they possess the proper genetic background to make them cancer susceptible—to respond with endometrial malignancy. There have been increasing reports in the recent literature pointing to the fulfillment of this expectation. Many authors have submitted reports increasing the impression of a relatively high incidence of corpus carcinoma associated with granulosa or theca cell tumors of the ovary.³³⁻⁴⁵ Especially noteworthy is the experience at the Mayo Clinic reported by Hodgson, Dockerty, and Mussey,⁴³ who found that in a group of thirty-eight postmenopausal patients with granulosa cell tumors,



Fig. 1.—($\times 250$) Fully developed cystic glandular hyperplasia.

eight, or 21 per cent, had accompanying corpus carcinoma; three also developed carcinoma of the breast. The experience at the Free Hospital for Women is comparable, for Pemberton⁴⁴ reported seven cases of corpus carcinoma which had developed in patients with functioning ovarian tumors, and Hertig⁴⁵ states that at least 18 to 20 per cent of the patients with granulosa cell or theca cell tumors of the ovary have associated carcinoma of the corpus.

The group of granulosa cell and theca cell tumors in our laboratory is small. Of nine patients with such functioning ovarian tumors, we have found only one with an associated endometrial carcinoma. We have studied the endometrium in each of these postmenopausal cases, however, and we have noted a striking degree of hyperplasia in many. Some are simply examples of fully

We have studied twenty human endometria with advanced degrees of hyperplasia produced by prolonged estrogen administration, and once again noted qualities which recurred with considerable frequency in the more active-appearing tissues: crowding of the glands into a lawless pattern, heaping up of the epithelium into pseudostratified masses, at times accompanied by intraglandular



Fig. 6.—(×250) Papillary budding pattern of intense hyperplastic activity.

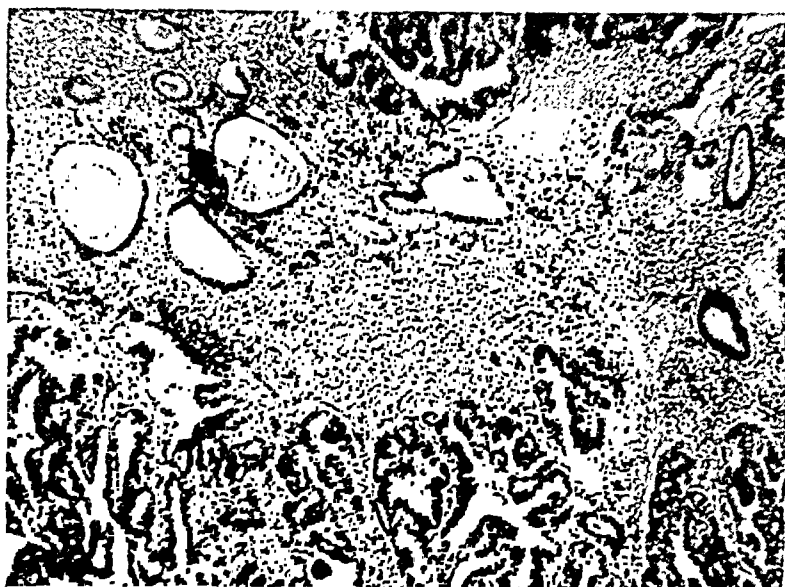


Fig. 7.—(×250) Papillary—appearing adenocarcinoma interspersed with areas of cystic glandular hyperplasia.

budding simulating a papillary pattern, paler, sometimes eosinophilic staining epithelium, and occasionally syncytiumlike epithelial masses on the surface; these metaplastic (adenomatous) areas are frequently focal. The accompanying microphotographs (Figs. 8 to 16) are examples of such activity in tissues from postmenopausal patients who have received prolonged medication with estrogens. We have not found this response to be related to the quantity of

(B) *Hyperplasia of the Human Endometrium Following Prolonged Estrogen Administration.*—Another human experiment has been set up in recent years by the widespread administration of estrogens to postmenopausal women. The relatively low cost of stilbestrol and the ease of its administration have made its general use promiscuous. Uterine bleeding provoked in postmenopausal patients by this medication has become such a commonplace occurrence

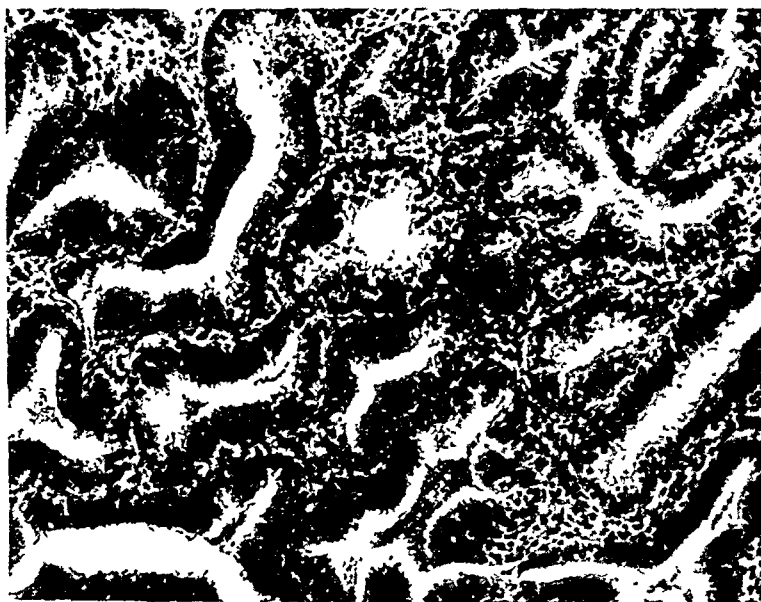


Fig. 4.—(×320) Area of crowded hyperplastic glands, with pseudostratification.



Fig. 5.—(×400) Adenomatous focus in hyperplastic endometrium.

that an idiomatic expression “stilbestrol bleeding” has found use on our gynecologic service when these cases are admitted for the necessary diagnostic curettage. We have not noted exceptional stimulating qualities in stilbestrol differing from those of other estrogenic substances, and the above-described frequent bleeding sequence is probably a mere reflection of its ease of administration, low cost and relative potency, and, therefore, of its frequent use.

ologically to estrogen stimulation.⁴⁶⁻⁴⁹ Smith⁴⁷ noted frequent stromal or theca cell activity in the ovaries of patients operated upon for corpus carcinoma. More recently Ayre and Bauld⁴⁹ reported evidence of thiamine deficiency in such patients, and they postulated resulting liver damage, failure of estrogen conjugation, and thus resultant high level of endogenous estrogen.

In spite of the common use of hormonal therapy for menopausal symptoms in recent years, there have been few reports of resultant uterine carcinoma.



Fig. 10.—($\times 360$) Eosinophilic staining gland with intraluminal budding.



Fig. 11.—($\times 320$) Early budding in focus of pale glands.

Gemell and Jeffcoate⁵⁰ reported three cervical carcinomas arising in a group of forty-three patients who had received estrogen therapy for senile vaginitis, but study of these histories suggests the probability that these lesions were present prior to the onset of treatment. Henry,⁵¹ in 1945, described two cases of marked endometrial hyperplasia following stilbestrol therapy whose pattern suggested malignancy and he stressed the importance of the persistent stimu-

the drug administered either in individual or total dosage, but rather to the persistent stimulus. None of these endometria could be called malignant, but all appeared very active, and some varied sufficiently from the well-known pattern of cystic glandular hyperplasia as to convince both pathologist and clinician that the patient's interests would best be served by prophylactic hysterectomy.

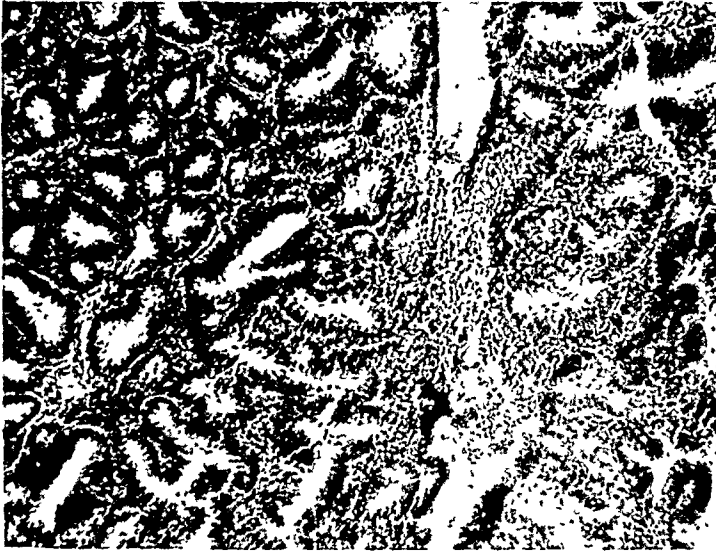


Fig. 8.—($\times 275$) Crowding of glands in intensely hyperplastic endometrium.



Fig. 9.—($\times 320$) Adenoma-like foci of crowded glands with pseudostratification.

It is important to point out that any presentation of a general endometrial pattern by a single microphotograph must necessarily be incomplete; Figs. 8 to 16 have been chosen in an effort to present an integrated picture of this process.

It is interesting to note the characteristics which these endometria share with those produced by the stimulus of granulosa cell tumors.

(C) *Adenocarcinoma of the Human Endometrium Following Prolonged Estrogen Administration.*—There have been occasional suggestions in recent years that spontaneous corpus carcinoma in human beings may be related eti-

Group I

We have studied five patients who have developed adenocarcinoma of the corpus uteri following prolonged estrogen administration. It is impossible to achieve proper controls in such a clinical investigation; it is therefore possible to dispute the relationship between the medication and the neoplasm in any individual case, in view of the well-known character of this tumor in remaining local for relatively long periods of time. However, these histories are extremely suggestive of an etiologic relationship, and the histologic data sup-

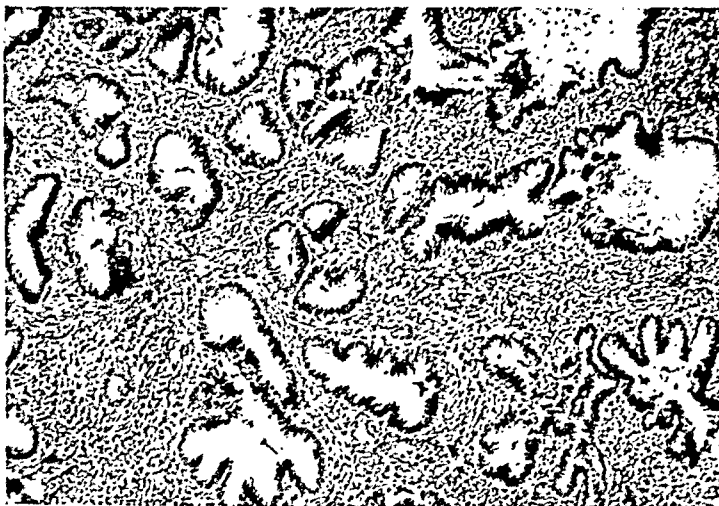


Fig. 14.—($\times 275$) Adenomatous hyperplasia fairly uniform.

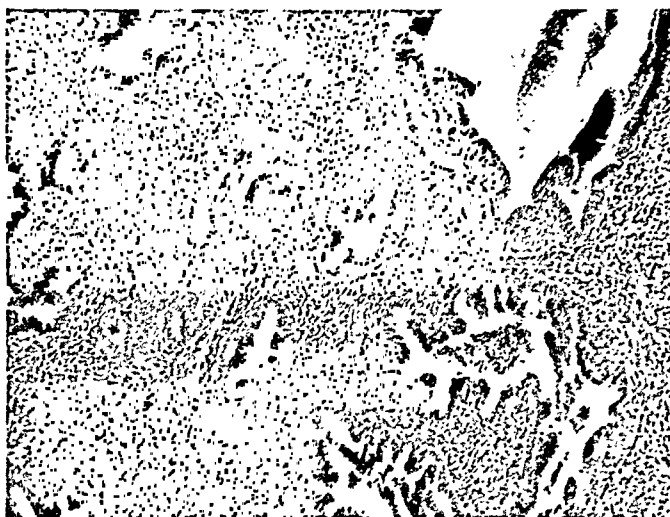


Fig. 15.—($\times 260$) Adenomatous hyperplasia with areas of intense activity.

porting them are also of a pattern which makes the suggestion strong enough to be significant and certainly to warrant further study. Brief abstracts of these cases are presented below.

CASE 1.—G. K., aged 56 years. In 1938, at the age of 48 years, radiation castration with x-ray therapy for menopausal bleeding was administered. Pelvic examination at that time was negative; no curettage

lus rather than quantity of dosage. Fremont-Smith, Meigs, Graham, and Gilbert,⁵² in 1946, reported the development of undoubted corpus carcinoma in a patient who had received estrogenic therapy over a long period of time; the history of this case certainly casts strong suspicion on this medication as an etiologic factor. It is well known that many experienced workers in the endocrine field have denied that estrogens possess carcinogenic properties in the human. Some have pointed to the widespread use of estrogens and the lack of precise evidence that malignancy has been produced by such administration.^{53, 54}

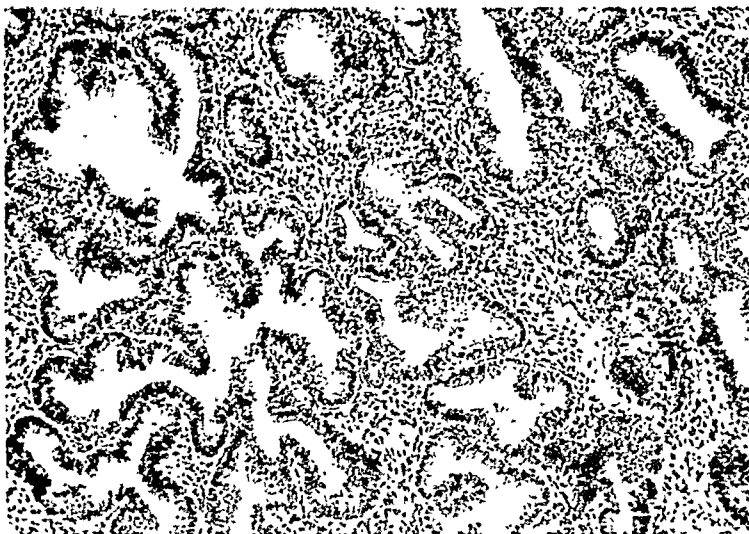


Fig. 12.—(×250) Scattered areas of adenomatous hyperplasia.



Fig. 13.—(×300) Early intraluminal budding in occasional adenomatous areas.

In this connection it is important to bear in mind the probable importance of the genetic factor in creating tissue susceptibility to abnormal growth stimuli, so that one should not expect more than an occasional union of the proper "substrate" and the proper stimulus in any general group of patients.

ing periods of amenorrhea and recurring menopausal symptoms. In December, 1941, at the age of 47 years, the menses ceased and the patient took almost daily stilbestrol for the next three years. In November, 1944, a curettage was performed because of onset of a blood-tinged vaginal discharge, and this revealed adenocarcinoma of the corpus uteri, as did sections of the subsequently removed uterus (Fig. 18).

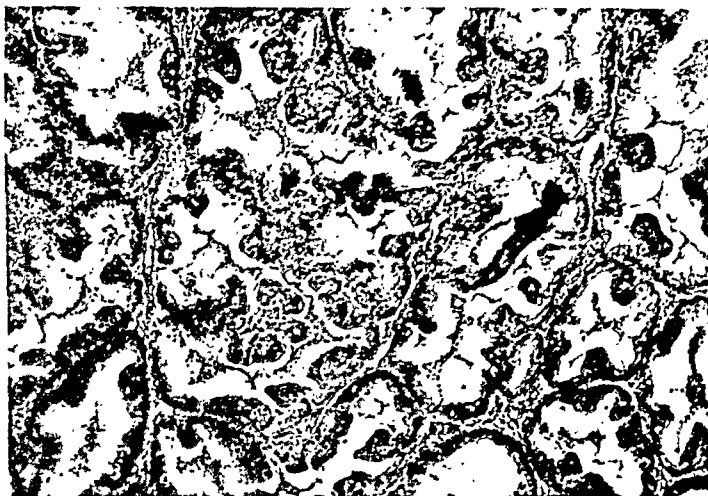


Fig. 18.—($\times 310$) Fully developed budding which gives tissue papillary appearance.

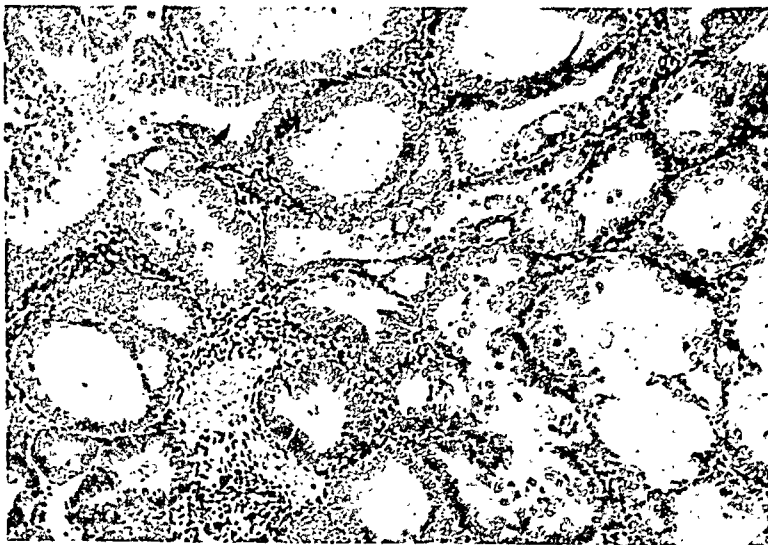


Fig. 19.—($\times 310$) Adenocarcinoma with budding pattern.

CASE 3.—E. B., aged 56 years. This patient is especially interesting in that her past history included an abdominoperineal resection for carcinoma of the rectum. An uneventful menopause occurred in 1939, seven years prior to her present admission. During this seven-year interval, the patient was treated constantly with estrogens for menopausal symptoms, and in recent years she had been taking almost daily stilbestrol.

She was admitted to the hospital in 1946 because of local recurrence of the rectal neoplasm, and vaginal bleeding. Curettage revealed a distinct, primary

was performed; no bleeding occurred following therapy. In May, 1941, a parathyroid adenoma was discovered and removed. In November, 1941, postmenopausal osteoporosis was diagnosed, and treatment with estradiol started in six-week courses followed by two weeks of rest. In March, 1942, estradiol was stopped and the patient was started on 1 milligram of stilbestrol daily for twenty-four days of each month; this therapeutic regime was continued for the next two years. In February, 1944, the dose was cut to 0.5 milligram because the patient had noted a monthly episode of bleeding.



Fig. 16.—($\times 360$) Adenomatous hyperplasia.



Fig. 17.—($\times 260$) Adenocarcinoma with budding mildly papillary pattern.

This withdrawal type of bleeding continued for the next several months until a curettage was performed in June, 1944. Sections of these curettings and those of the subsequent hysterectomy specimen revealed adenocarcinoma of the corpus uteri. Fig. 17 illustrates a characteristic area of this malignant endometrial tumor.

CASE 2.—S. S., aged 50 years. In 1934, at the age of 40 years, this patient came under gynecologic supervision for amenorrhea. She received intermittent injections of estrogenic substances during the next seven years because of vary-

were performed (Figs. 21 and 22). The surgical specimen not only confirmed the diagnosis of malignancy of the endometrium, but also contained metastatic disease in both ovaries.

The histologic pattern of these malignant endometria developing in patients who had received prolonged estrogen therapy is most interesting in that it bears considerable resemblance to the hyperplastic and metaplastic endometria described above. In some areas one gains the impression that this process is but an intensification of an atypical adenomatous pattern of hyperplasia. One can

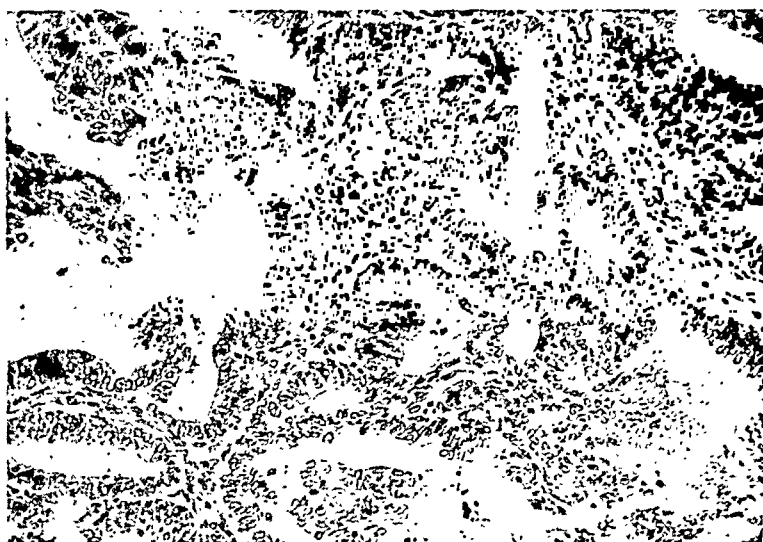


Fig. 21.—($\times 300$) Adenocarcinoma with papillary qualities.



Fig. 22.—($\times 360$) Papillary, budding glandular foci, some with pale staining qualities.

see typical cystic glandular hyperplasia, atypical (metaplastic) hyperplasia, and adenocarcinoma side by side in some sections. The multifocal malignant processes, often separated by areas of typical hyperplasia, present the picture of a generally stimulated tissue which has responded more intensely in some areas. There is a characteristic pattern which constantly recurs through these tissues; it is almost papillary in form; it shares morphologic properties with other tissues known to have been stimulated by estrogens.

adenocarcinoma of the corpus, unrelated histologically to the rectal tumor. Fig. 19 illustrates the characteristic pattern of this endometrial neoplasm.

CASE 4.—M. W., aged 60 years. A spontaneous uneventful menopause occurred in this patient at the age of 48 years. This was notable only in that the patient received a course of radiation therapy to her thyroid for hyperthyroidism. For three years following the cessation of her menses, she received estrogenic therapy for menopausal symptoms. During the succeeding six years no hormonal treatment was given, then, at the age of 57 years, her physician resumed estrogenic and vitamin therapy. This was continued for three years, during which time she noted intermittent stimulation of her breasts.

In 1946, at the age of 60 years, a curettage was performed because of the onset of slight vaginal bleeding, and this revealed a typical adenocarcinoma of the uterine corpus (Fig. 20).

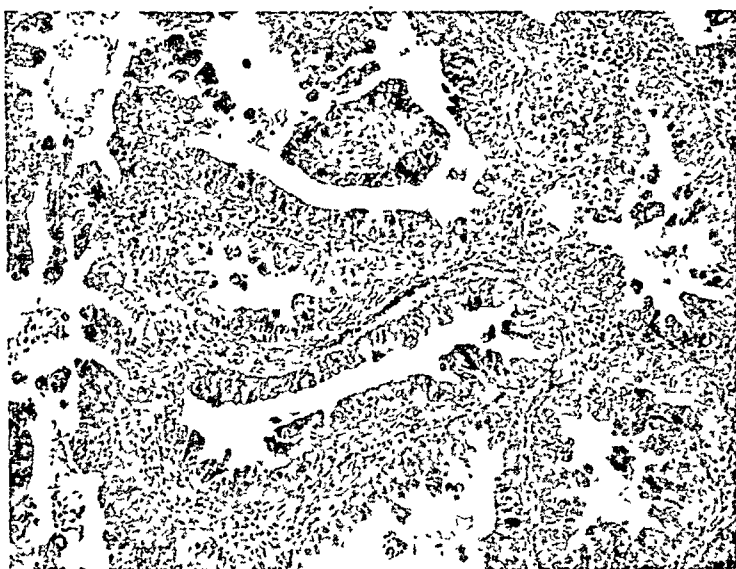


Fig. 20.—(×260) Adenocarcinoma with focal appearance of intense adenomatous hyperplasia.

CASE 5.—S. M., aged 41 years. This patient first came under gynecologic supervision in 1932 when she consulted her physician for amenorrhea of approximately one year's duration. She was then 34 years old. During the succeeding three years, she received intensive estrogenic therapy, with periods of rest and the occasional addition of progesterone. She continued to have long periods of amenorrhea, though there were intermittent scant menses hardly more than spotting. Occasional endometrial biopsies were taken; they revealed normal endometrium without secretory change. In 1936 and 1937, she received little endocrine therapy, but in 1938 this was resumed: it was not given regularly throughout this year; emphasis was placed on progesterone. From May to September, 1938, menses were fairly regular, but irregular spotting recurred thereafter. In March, 1939, significant noncyclic bleeding occurred, and a curettage was performed; this revealed endometrial hyperplasia and metaplasia, and areas which were interpreted as malignant. Because of the clinical impression that the atypical endometrial pattern represented an endocrine effect rather than malignancy, no further treatment was offered until September, 1939. At that time repeat curettage demonstrated adenocarcinoma beyond any reasonable doubt, and a complete hysterectomy and bilateral salpingo-oophorectomy

hyperplasia of the endometrium. At the age of 30 years, another episode of profuse vaginal bleeding brought the patient into our hospital, where curettage revealed markedly hyperplastic endometrium with metaplastic areas (Fig. 23). Because of the intense picture of activity in this endometrium, and because her repeated blood loss was incapacitating, a hysterectomy was advised. Study of the hysterectomy specimen revealed markedly active hyperplasia, and also localized areas of adenocarcinoma (Fig. 24).

CASE 7.—A. C., aged 38 years. This patient came under observation in 1936 at the age of 32 years because of enormous obesity, sterility, and long-standing irregular menses. There were frequent episodes of amenorrhea followed by persistent bleeding. In 1936 and 1937, the patient received prolonged estrogenic therapy, but in 1938 and 1939, there was no significant endocrine medication. Following weight reduction, normal menses were resumed in 1939 and continued in 1940 and 1941; infrequent estrogen, corpus luteum, or thyroid preparations were offered. After seven months of normal menstrual cycles menorrhagia was resumed in April, 1942, and curettage in June revealed adenocarcinoma of the corpus (Fig. 25).



Fig. 25.—(×275) Adenocarcinoma with papillary budding foci.

CASE 8.—T. L., aged 45 years. This patient sought gynecologic care for vaginal discharge of three months' duration, five years after a normal menopause. From January to May, 1937, estrogenic therapy was given for senile vaginitis; irregular staining of a withdrawal type was noted. This inconstant spotting continued from June to October, in spite of discontinuation of therapy, and curettage in October revealed adenocarcinoma of the corpus (Fig. 26).

CASE 9.—G. J., aged 41 years, entered gynecologic supervision in September, 1940, at the age of 40 years, approximately one year after a normal menopause. Pelvic examination revealed no abnormality. Stilbestrol therapy for menopausal symptoms was started and it was continued through October, November, and December of that year. After a four-week interval of rest, it was resumed in January, 1941. In February, the patient complained of lower abdominal pain; examination revealed a large cystic mass filling the cul-de-sac. Laparotomy was performed and hysterectomy with bilateral salpingo-oophorectomy readily accomplished. Pathologic study revealed endometriosis of the right ovary with adenocarcinoma probably arising from an endometrial cyst (Fig. 27).

Group II

We have also studied three other corpus carcinomas and an ovarian adenocarcinoma whose development may have been accelerated by estrogen administration and their histologic pattern modified. They are important because endocrine therapy obscured or delayed diagnosis; there is no significant evidence in these cases that the administered estrogenic substances initiated the abnormal endometrial growth. Resemblance of these tissues to each other, however, and to the patterns described above, lends the impression that the endocrines may have modified them.



Fig. 23.—(×400) Budding pattern of intense hyperplastic activity in crowded glands.

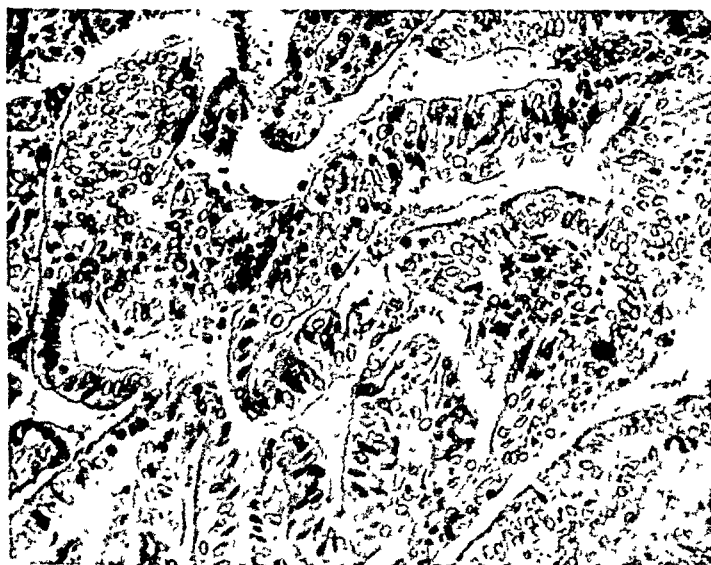


Fig. 24.—(×400) Localized area of well differentiated adenocarcinoma.

CASE 6.—F. Y., aged 30 years. This patient presented a six-year history of sterility, repeated episodes of profuse bleeding, and varying courses of endocrine therapy. Curettage had been performed on three occasions before her final treatment; the last of these, three years before final admission, revealed

Herrell, in 1939,⁴⁶ described "persistent proliferative endometrium" as a frequent accompaniment of corpus carcinoma, but did not designate this pattern as a hyperplastic one. It is apparent, however, that his studies suggested a picture of estrogenic endometrial stimulation, for they led him to the conclusion that estrogens played an etiologic role in the development of endometrial carcinoma.

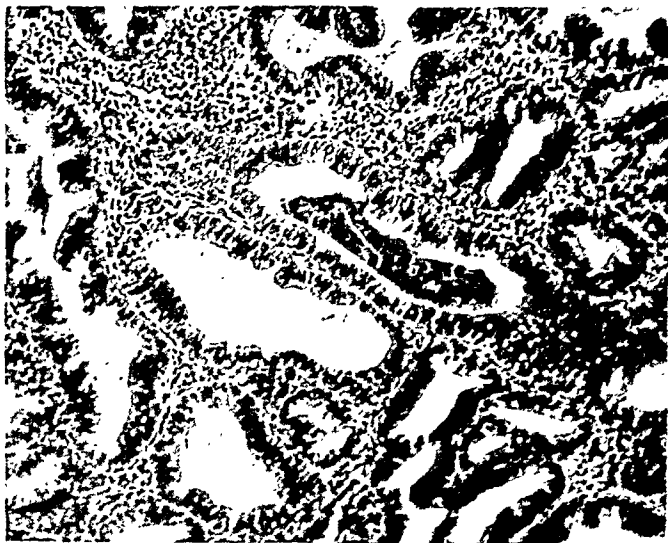


Fig. 28.—(×360) Adenomatous focus of crowded glands.

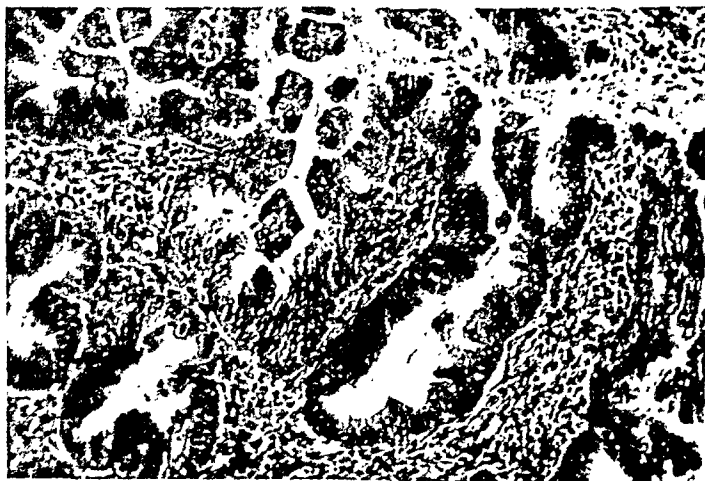


Fig. 29.—(×380) Papillary budding pattern of glands.

Others have doubted the importance of endometrial hyperplasia in the development of corpus carcinoma.⁶⁴⁻⁶⁷ Maek, in 1929,⁶⁸ and Hintze, in that same year,⁶⁹ reported follow-up studies of patients with endometrial hyperplasia with few examples of later carcinoma.

In an effort to evaluate the endocrine background of patients with corpus carcinoma, we have studied their reproductive histories, and we have noted deviations which suggest abnormality of internal secretions: an increased incidence of infertility, delayed menopause, and menopausal bleeding.⁷⁰ The

(D) *Relation of Hyperplasia of the Endometrium to the Development of Corpus Carcinoma.*—It has been well established that persistent unopposed estrogenic stimulation of the endometrium is responsible for the production of the characteristic pattern of cystic glandular hyperplasia. A possible relation between this hyperplasia and adenocarcinoma of the endometrium has been sought for some time without general agreement concerning the interpretation of data or conclusions submitted. There have been recurrent reports of corpus carcinoma developing in patients with coexistent or prior hyperplasia.⁵⁵⁻⁶¹



Fig. 26.—(×300) Adenocarcinoma with papillary pattern.



Fig. 27.—(×275) Papillary adenocarcinoma of ovary with endometrial pattern.

Taylor, in 1932,⁶² and Novak and Yui, in 1936,⁶³ reported their studies of this problem, and they concluded that there was a developmental relationship between endometrial hyperplasia and carcinoma. The latter authors emphasized the importance of hyperplasias persisting into the postmenopausal age group; they described atypical patterns of hyperplasia of a type which we have noted in patients who have continued to the full evolution of neoplasm, and which we have also seen in endometria stimulated by administered estrogens (see above).

Thus, these individuals who apparently have an increased susceptibility to the later development of corpus carcinoma demonstrate a significant frequency of endocrine stigmata of a type which has been associated with infrequent ovulation, and probably noncyclic persistent unopposed estrogen stimulation.

Certainly every laboratory of gynecologic pathology frequently encounters hyperplastic endometria which suggest a stage in the development of carcinoma;

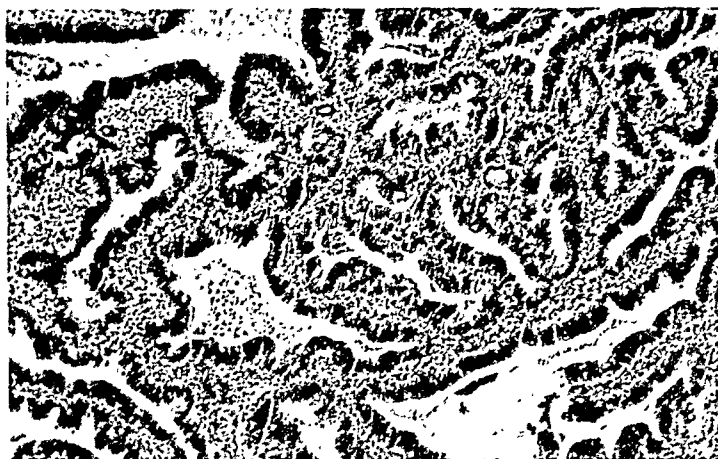


Fig. 32.—($\times 250$) Adenomalike area of crowded glands.



Fig. 33.—($\times 360$) Budding papillary glandular pattern.

in some instances one can observe areas of cystic glandular hyperplasia surrounding a true endometrial adenocarcinoma. We wish to call attention to the pattern of atypical (adenomatous) hyperplasia which is sometimes encountered in patients who have suffered repeated episodes of "functional bleeding" (Figs. 28 and 29): it is a papillary pattern of glandular activity, of an identical nature to that which has been described above as an end result of endogenous (functioning ovarian tumors) or exogenous (estrogen therapy) estrogen stimulation. The histologic picture in some of these cases is very difficult to distinguish from frank adenocarcinoma. Furthermore, it is interesting to note that in some patients with repeated episodes of bleeding who have progressed to the development of true adenocarcinoma, the pattern of the pre-existing hyperplasia is a

latter observations have also been reported by Crossen and Hobbs,⁷¹ and Randall⁷² in their clinical investigations of adenocarcinoma of the corpus.

Another study in our clinic investigating the nature of the menopause in relation to subsequent carcinoma⁷³ also suggested an endocrine factor. It revealed that among women who had been treated radiotherapeutically for benign causes of bleeding at the menopause, there were observed three and one-half



Fig. 30.—($\times 380$) Focus of pale staining, budding glands.

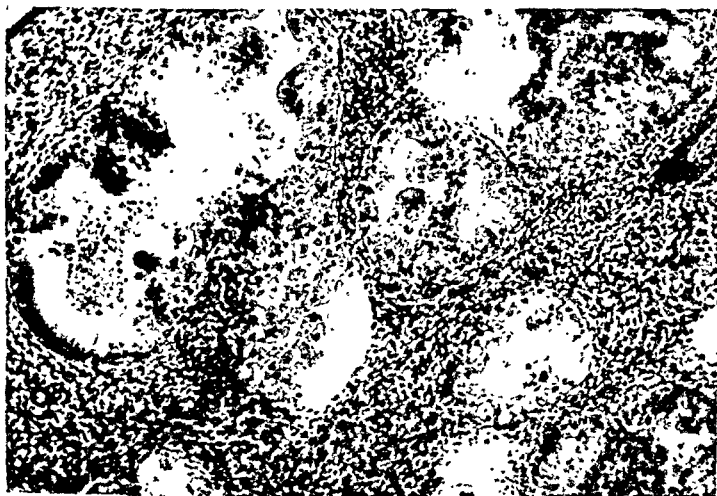


Fig. 31.—($\times 360$) Adenomatous focus in a generally hyperplastic endometrium.

times as many subsequent corpus carcinomas as would be expected in a similar sampling of the general population. In surveying the endometria obtained from individuals who have required treatment for benign causes of bleeding at the menopause, we have noted hyperplasia in 31 per cent. It would appear that repeat curettage at varying stages of the bleeding episodes might increase this proportion of hyperplasia, for there may be irregular shedding of this tissue.⁷⁴ At any rate, the number that showed progesterone influence was small (13 per cent). There is some evidence to suggest that these menopausal patterns may persist asymptotically into the postmenopausal period.^{75, 76}

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similar one to that described above with focal metaplastic areas (Figs. 30, 31, 32, and 33). In some cases one can distinguish several stages of apparent development of the neoplasm in the same endometrium (Fig. 34). These histologic considerations suggest to us the probability that there does exist a type of endometrial hyperplasia which can progress to adenocarcinoma under suitable conditions.



Fig. 34.—($\times 275$) Foci of adenomatous hyperplasia of varying intensity.

Summary and Conclusions

1. A pattern of adenomatous hyperplasia of the endometrium is described which bears a constant relation to estrogen stimulation in both benign and malignant tissues.

2. We have presented data concerning this endocrine-tumor relationship in four related groups: (a) Endometrial hyperplasia produced by granulosa cell tumors. (b) Endometrial hyperplasia produced by prolonged estrogen administration. (c) Endometrial adenocarcinoma arising in patients receiving prolonged estrogen administration. (d) Endometrial patterns in patients with recurrent episodes of "functional bleeding."

3. The well-defined histologic pattern recurring in these related groups of tissues suggests that endogenous or exogenous estrogens play a role in the development of corpus carcinoma. We have called attention to a type of endometrial hyperplasia which is a cancer precursor.

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FATAL ECLAMPSIA

A Clinical and Anatomic Correlative Study

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THIS paper represents a summary of all fatal cases of eclampsia which were examined at autopsy in the Department of Pathology, Duke Hospital, during the period 1930 to 1946. Although primary emphasis has been placed upon the pathologic aspects of these cases, it is believed that a correlation of the clinical history and the postmortem findings may prove most useful in adducing conclusions of significance to both clinician and pathologist.

During this period there were 33 necropsies performed in cases of fatal eclampsia. Our criteria for determination of eclampsia were the appearance of the usual signs of severe toxemia in a gravid patient during the latter half of her gestation, together with a generalized motor seizure. It is true that eight of these patients never had convulsions even up to their exitus.* The adjudgment of these eight cases as eclampsia depended upon the finding of focal hyaline or fibrinoid necrosis in the liver with a history of severe toxemia. Therefore the criteria for classification in this category are the following: (1) severe toxemia with generalized motor seizure during life in the last half of pregnancy, or (2) severe toxemia resulting in death, autopsy revealing focal hyaline hepatic necroses.

The occurrence of convulsions in pregnancy and especially in toxemia has been well discussed by Burnett.⁴ He expresses the thought that, with identical degrees of albuminuria, elevation of blood pressure, and other signs of toxemia, one patient will present eclamptic convulsions, while another will not. It is his opinion, therefore, that a varying degree of nervous instability exists which plays a part in causing the eclamptic fit.

This is in keeping with the concept that for a generalized motor discharge of the central nervous system there exists a very definite threshold as in any other physiologic or pathophysiologic process in the body. This threshold varies, so that what may be adequate stimuli in one patient with toxemia may fall short of the threshold in another.

Clinical Analysis

A great number of reports appear in the literature concerning the vital statistics on eclampsia.^{5, 6} As might be expected with such a small series as this, there are percentage variations from those reports which draw upon hundreds of nonfatal cases. Therefore it is doubtful that the differences are significant.

*This occurrence has been described by many authors.¹⁻³

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previous toxemias of pregnancy. The stress of such toxemias upon the organism cannot be denied; whether any damage residual to that stress remained, however, is not certain. Finally, we may postulate that eclampsia *per se* is a much more severe condition and more likely to prove fatal in the multiparous woman. However, the latter hypothesis awaits further study.

The factor of racial distribution presents itself in this group of patients. Twenty-one of the cases occurred in Negro women; one was Indian. This is probably not evidence of racial susceptibility, but rather reflects the nature of the local population. It cannot be ignored that a gravid Negro woman probably faces greater handicaps in enduring pregnancy than a white woman of equal economic status. Moreover, negligence in seeking prenatal care and in executing proper medical instruction is a major contributing factor among these people. The racial incidence is demonstrated in Table III.

TABLE III. RACIAL INCIDENCE

| | NUMBER OF CASES | PER CENT |
|--------|-----------------|----------|
| White | 11 | 33 |
| Negro | 21 | 64 |
| Indian | 1 | 3 |

The importance of prenatal care arises in this series of cases. Surprisingly enough, ten (30 per cent) of these patients had some prenatal medical attention. This was administered, for the most part, by a local physician in a rural area. In only one case (28) was there a history of frequent visits to the doctor during gestation. This patient was perfectly well until twenty-four hours before admission, when the onset of the toxemia was abrupt and most severe. The nature of this case is of greatest interest and will be discussed in some detail later.

Family history here, as in any other disease entity, may or may not be of significance. Seven (21 per cent) of these patients had a family history of hypertension. Of particular interest is the patient in Case 5, who had three sisters dying of fatal eclampsia.

Of much greater interest, however, is a review of the past histories among the 16 multiparous patients. Eleven had shown the signs and symptoms of pre-eclamptic toxemia in at least one of their previous pregnancies. Five of these 11 patients had had clinically recognized eclampsia previously.

TABLE IV. INCIDENCE OF PREVIOUS TOXEMIA

| | NUMBER OF CASES | PER CENT OF ALL MULTIPARAS |
|-----------------------|-----------------|----------------------------|
| Pre-eclamptic toxemia | 6 | 38 |
| Eclampsia | 5 | 31 |
| Total toxemia | 11 | 69 |

The past histories of the primiparous patients were of no significance.

A review of the symptoms prior to admission is illustrated in Chart 2. It will be seen that headache, edema, and convulsions were most outstanding. Twenty of the patients had at least one generalized seizure prior to admission. Of the remaining 13, five had seizures subsequent to their arrival. The other eight, as has been mentioned previously, never had convulsions prior to death. However, these fulfill our criteria for eclampsia by demonstrating focal hyaline necroses of the liver.

The age range was 13 to 41 years, with a mean of 24.1 years. Eighty per cent of the patients lie within the range of 15 to 30 years. As might be expected, the average age of the primiparous patient was considerably less than that of those who had had previous pregnancies: 19.7 years, as compared with 29 years. This is represented in Table I.

TABLE I. AVERAGE AGES

| | YEARS |
|--------------|-------|
| Entire group | 24.1 |
| Primiparas | 19.7 |
| Multiparas | 29.0 |

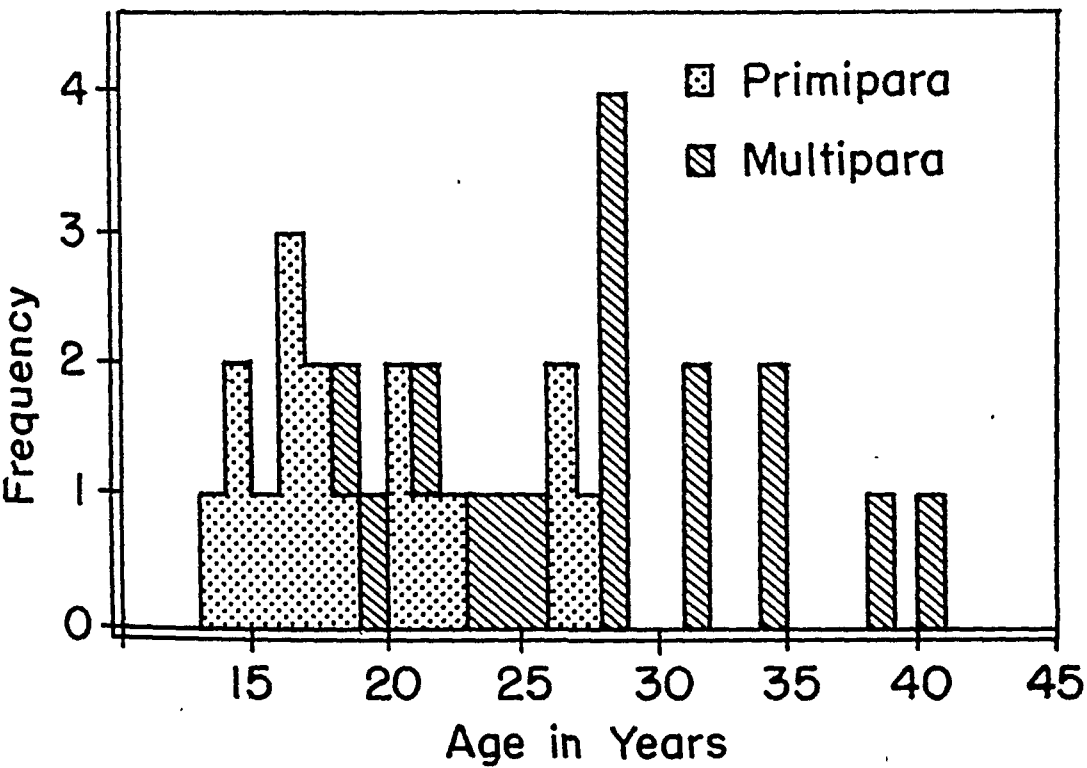


Chart 1.—Age, frequency, and parity distribution.

The parity of eclamptic patients has always been a great source of interest and speculation. Our figures fail to confirm the fact that the primiparous patient is more subject to severe eclamptic toxemia. Seventeen (51.5 per cent) of these patients were primiparas, while sixteen (48.5 per cent) had had previous pregnancies. These figures are at considerable variance from those given for eclampsia in general. DeLee¹ reports a ratio of primiparas to multiparas of 3:1, while Stander² quotes Hinselmann with a ratio of 6:1. Our ratio for fatal eclampsia is 1.1:1.

The significance of this considerable difference must be interpreted in the light of several factors. The first is the observation that the multiparous group is about ten years older than those pregnant for the first time. Secondly, as we will soon show, an appreciable portion of these multiparous patients had had

TABLE II. PARITY

| | NUMBER OF CASES | PER CENT |
|------------|-----------------|----------|
| Primiparas | 17 | 51.5 |
| Multiparas | 16 | 48.5 |

Of secondary frequency among the symptoms were recent nausea and vomiting, visual disturbances, and abdominal pain. These were present in about one-third of the cases. Additional symptoms consisted mainly of dyspnea, oliguria, and dizziness.

The principal physical findings on admission are displayed in Chart 3. Hypertension was present in 32 cases, the thirty-third being in shock (blood pressure 80/40) on arrival. This patient expired in the emergency room within twenty minutes. Our criterion for hypertension is a blood pressure in excess of 140/90.

Twenty-five patients (78 per cent) demonstrated generalized edema, while 19 (69 per cent) were in coma. A tachycardia of 100 or more existed in 20 patients. Pulmonary edema was present in 11 patients. Fever of 38° C. or higher was found in nine (28 per cent); hyperpnea of 30 respirations per minute or more was noted in eight. Four patients were cyanotic.

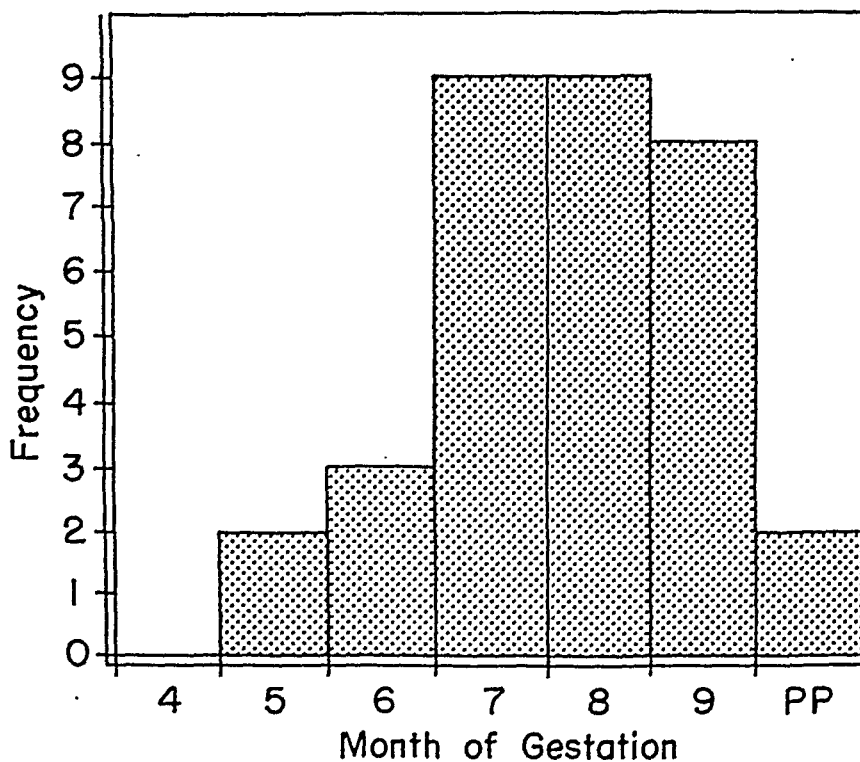


Chart 4.—Duration of pregnancy.

Since the blood pressure is an all-important sign in toxemia, an attempt has been made to classify the degree of hypertension as mild, moderate, or severe on the following basis:

1. Severe hypertension: either a systolic pressure over 200 or a diastolic pressure over 120
2. Moderate hypertension: either a systolic pressure between 160 and 200, or a diastolic between 100 and 120
3. Mild hypertension: either a systolic between 140 and 160, or a diastolic between 90 and 100.

On the basis of the above criteria, the hypertension can be classified as severe, 58 per cent; moderate, 30 per cent; and mild, 9 per cent of the cases. This is demonstrated in Table V.

The duration of the various pregnancies at the time of hospital admission are represented in Chart 4. It will be seen that two cases were post partum,

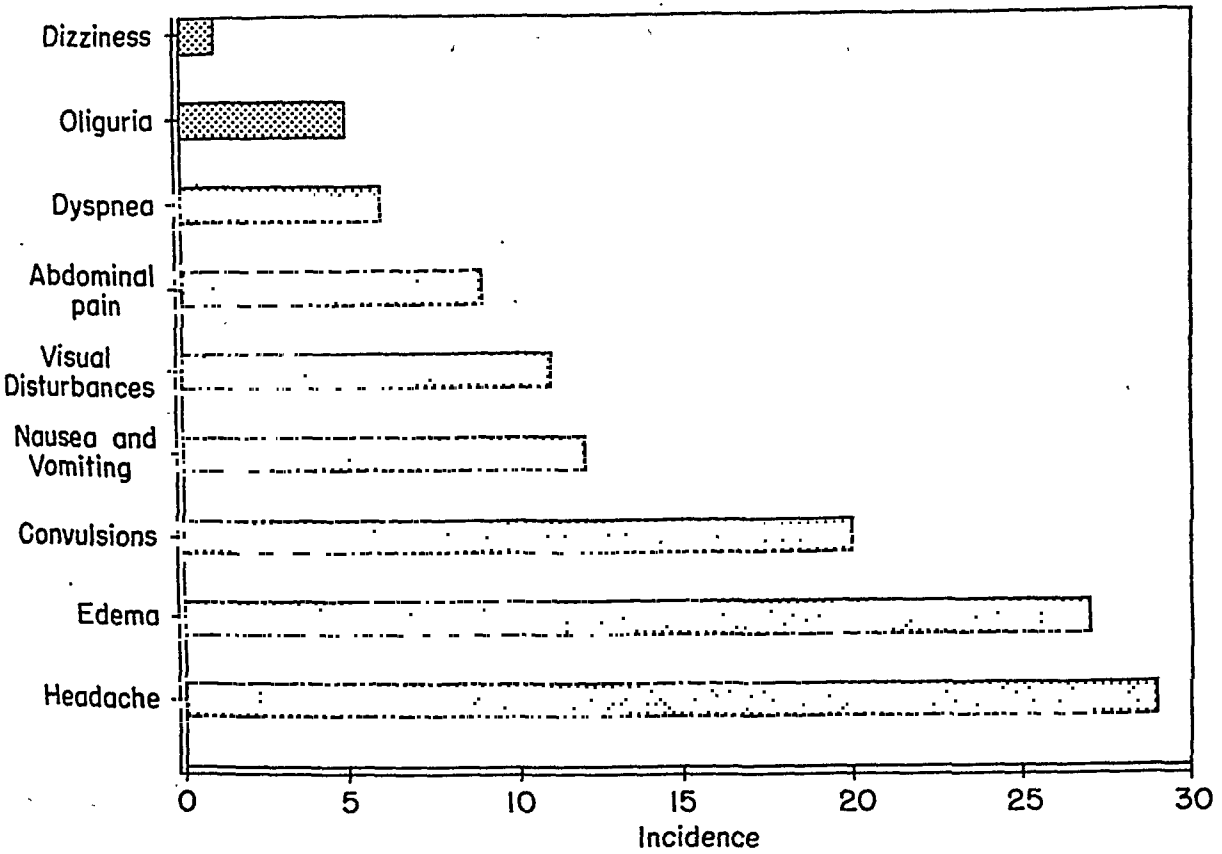


Chart 2.—Symptoms prior to admission.

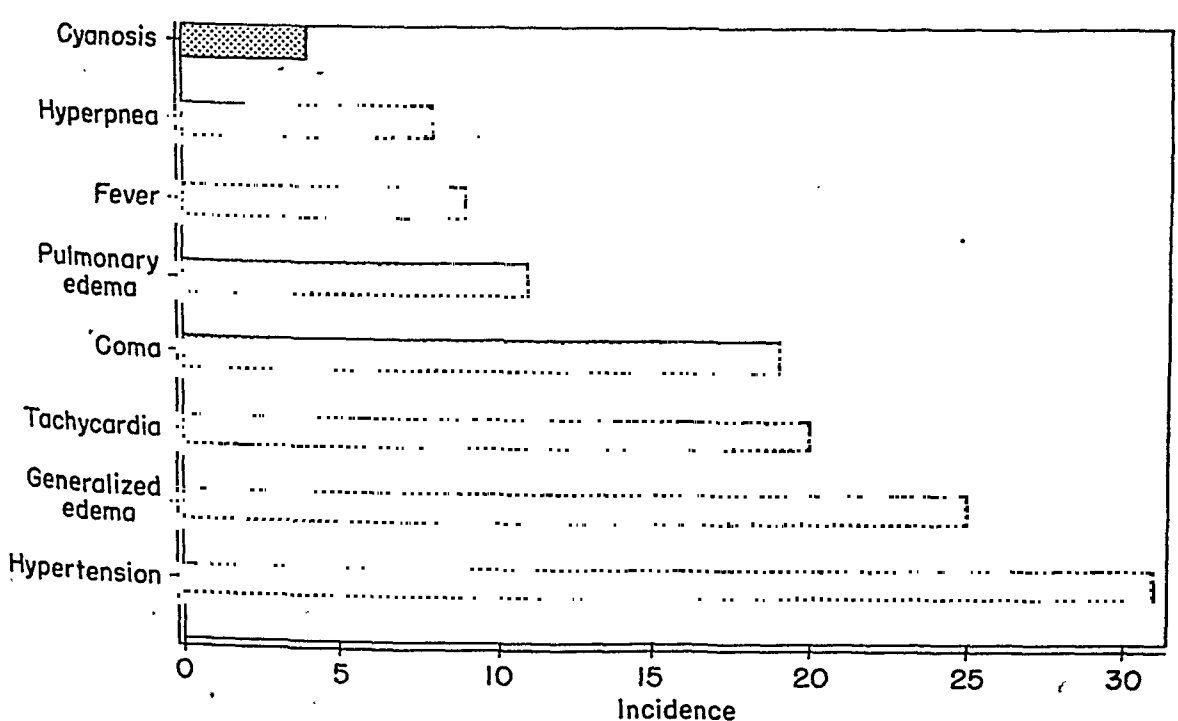


Chart 3.—Physical findings on admission.

uric acid, however, are of considerable more significance. The mean value here is 5.88 mg. per cent.

The two graphs have been centered by placing the 4 mg. per cent value for uric acid over the 40 mg. per cent value for NPN, taking these two as the upper limits of normal. It will be seen that the peak of the graph for uric acid is considerably to the right of that for the non-protein-nitrogen.

Plasma protein determinations were performed in seven patients. The average total plasma protein was 4.97 Gm. per cent with an albumin-globulin ratio of 0.84. This is compared with those values obtained by Møller-Christensen and Thygesen,⁸ who determined these values in a series of nonfatal eclampsia as a total protein of 5.61 Gm. per cent and an A/G ratio of 1:10. It will be noted that our values are considerably lower.

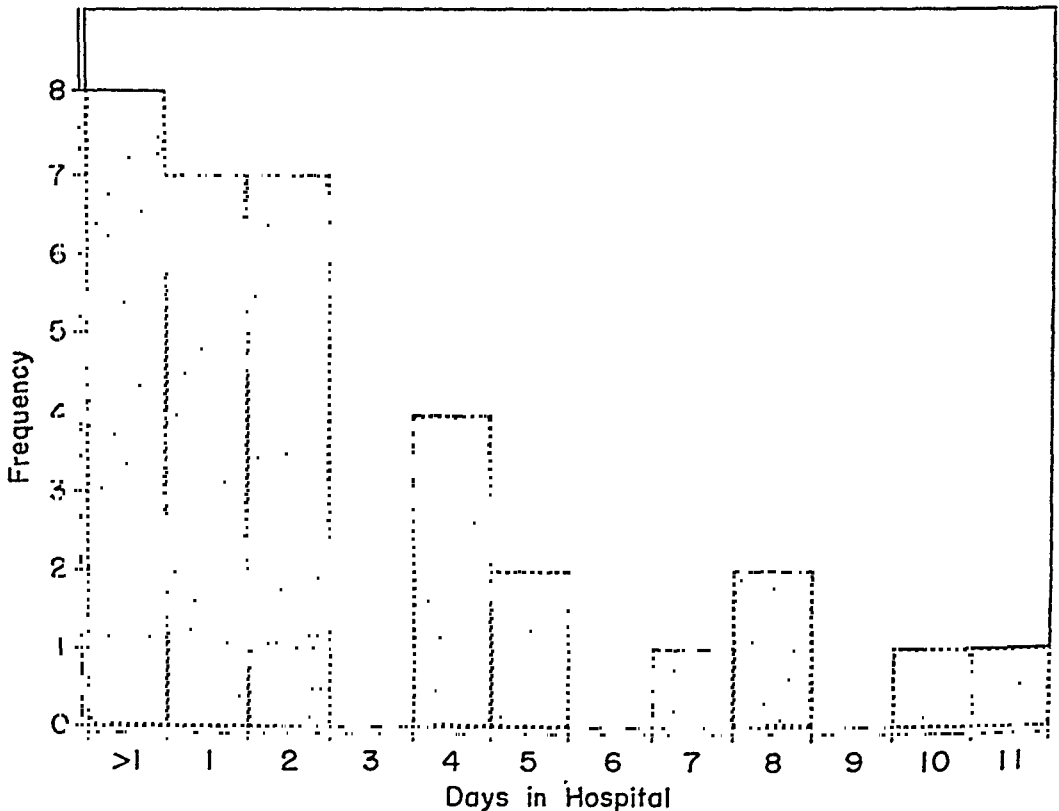


Chart 6.—Hospital stay prior to death.

The duration of stay in the hospital prior to death is of some interest. Eight patients expired within the first twenty-four hours, and seven subsequent deaths occurred on each of the two succeeding days. Therefore, within the first 72 hours, 22 (67 per cent) had expired. The arithmetic average for the group was 2.88 days, but this is considerably distorted by two cases (17 and 24), who remained alive 10 and 11 days, respectively. The distribution is given in Chart 6.

By summarizing the essential clinical aspects of these fatal cases of eclampsia, we can create a composite picture of the average patient.

If a primipara, the patient is about 19 years of age, Negro (in this area only), and has had at least one convulsion prior to admission. During the few days or weeks preceding admission she has experienced increasingly severe headaches and edema. She may also complain of one of the three following symptoms: recent nausea and vomiting, visual disturbances, or abdominal

TABLE V. DEGREE OF HYPERTENSION ON ADMISSION

| | NUMBER OF CASES | PER CENT |
|----------|-----------------|----------|
| Mild | 3 | 9 |
| Moderate | 10 | 30 |
| Severe | 19 | 58 |
| Shock | 1 | 3 |

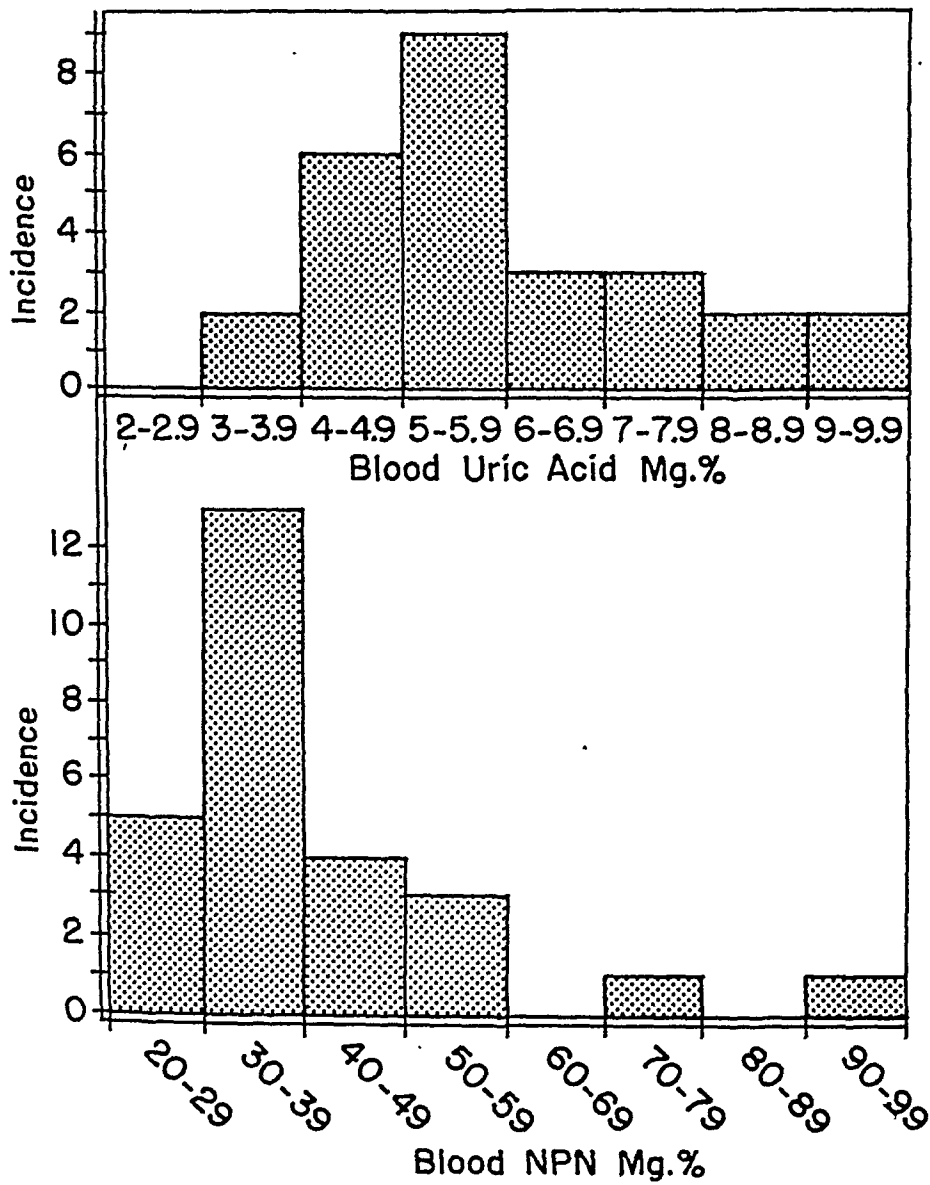


Chart 5.—Blood chemistry on admission.

and that the peak frequency was in the eighth calendar month. The average duration of pregnancy for this series was 7.6 months.

The blood chemistry findings are of considerable interest. Kaplan,⁷ in his paper on blood chemistry studies in normal pregnancy and eclamptogenic toxemia, reports increases in both the non-protein-nitrogen and the uric acid levels in the blood in eclampsia. Inspection of Chart 5 will reveal that the non-protein-nitrogen is only slightly increased, the average determination being 37.2 mg. per cent. This is somewhat distorted by two high values of 91 and 70 mg. per cent in Cases 5 and 17, respectively. Therefore, in general, we can say that the increase in non-protein-nitrogen is minimal. The readings for

the same cellular reaction. However, Case 24 demonstrates multiple focal fibrinoid necroses limited to one lobe without cellular response. This lack of leucocytic reaction prevails in the majority of cases in which liver necrosis was present.

This observation has led us to believe that the majority of the necroses are of very recent origin.

Careful examination of the liver sections on those multiparous patients who had a history of previous toxemia fails to reveal any evidence of scarring. This suggests that whatever hepatic lesions occurred have healed without scarring and that the process is reversible.

It cannot be denied that gross impairment of function of an organ can exist without any visible anatomic alteration. However, in the presence of widespread areas of normal-appearing hepatic tissue, in many cases it is most difficult to explain the functional changes in eclampsia on the basis of the hepatic lesions.

Kidney.—Renal changes have been observed by a variety of authors. Löhlein⁹ first described the glomerular changes which he construed to be those of glomerulonephritis. Later, Fahr¹⁰ differentiated these from glomerulonephritis and called them glomerulonephrosis. Finally, Bell,¹¹ in 1932, clearly defined these changes and considered them characteristic of eclampsism.

The glomeruli are usually avascular and devoid of erythrocytes, although at times they may be the seat of acute congestion. Congestion is evident when there is pronounced heart failure and accompanying congestion of all of the abdominal viscera. Congestion may also be seen occasionally when septicemia is present. There is also a definite increase in the endothelial cells in the glomerulus, as indicated by the increase in nuclei present. Also, one may see fibrinoid or hyaline necrosis of a glomerular tuft, which may spread to involve the entire glomerulus. The capillary basement membrane is conspicuously thickened and may even be duplicated.

In the preglomerular arteriole there is swelling of the wall, which may then undergo necrosis or hyalinization. If it be necrosis, there is usually thrombus formation which may extend further into the glomerulus itself.

Occasionally there is fibrosis beneath Bowman's capsule, but this is not a prominent feature.

Tubular changes have long been described as the prominent renal lesion in eclampsia, and some authors¹² still consider them the outstanding feature. Zimmerman and Peters,¹³ in reviewing fatal cases of toxemia, laid considerable stress upon tubular changes. However, the incidence of pyelitis and pyelonephritis in their series was extremely high. The presence of retrograde infection and inflammation from the renal pelvis undoubtedly alters the tubular picture.

We have not been impressed by the tubular changes. It is true that there is cloudy swelling and some colloid degeneration of the tubular epithelium, but this is a highly nonspecific reaction and is seen in a wide variety of disease processes. Emphasis in the past has been placed on the presence of fat droplets within the tubular epithelium. Fat stains have been performed upon a number of these sections, and the presence of fat has been demonstrated. However, it is far less prominent than is usually seen in chronic glomerulonephritis. Indeed, in some of these sections the fat was more prominent in the glomeruli than it was in the tubular epithelium.

Erythrocytes are commonly seen in the tubules. It is our impression that this is most prominent when there is glomerular congestion.

Changes in the renal pelvis in this series are of minor importance. Only two cases (1 and 26) show evidence of pyelitis, and this is of a chronic, apparently inactive nature.

pain. Physical examination reveals that she has hypertension and generalized edema and is in a comatose condition. Tachycardia and pulmonary edema may or may not be present.

If a multiparous patient, she is about 29 years of age, either white or Negro, and has had the signs and symptoms of pre-eclamptic toxemia during a previous pregnancy. There is one chance in three that she has had a previous attack of eclampsia. She, too, is comatose and demonstrates hypertension and edema. In all probability, she has had convulsions prior to admission.

Both patients will demonstrate a slight increase in blood non-protein-nitrogen and a definite increase in blood uric acid. Total plasma proteins will be reduced, and the albumin-globulin ratio markedly reduced. Death will ensue in about two days.

Anatomic Lesions

In the following section are presented the pertinent anatomic changes in the above cases. This will be followed by an attempted correlation of the various lesions in an effort to gain insight into the pathogenesis of this disease syndrome.

Liver.—The liver is the seat of an important pathologic change. The lesion most frequently encountered is a focal hyaline or fibrinoid necrosis of the liver cells, usually, but not necessarily, in the periportal areas.

The most characteristic aspect of this lesion is its variability in extent and severity. At times, it is utterly impossible to demonstrate hepatic necrosis, although its presence cannot be eliminated without study of serial sections of the entire organ. At other times the process is extremely widespread so that viable or normal appearing liver tissue is relatively scarce. Occasionally the disease process may be extremely widespread in one lobe of the liver, while the remainder appears relatively unaffected. Generally speaking, the majority of the cases show an affection between these two extremes.

In an effort to correlate the absence of hepatic necrosis with the duration of symptoms prior to death, Cases 2, 8, and 19 are examined. The patient of Case 2 presented her first symptom, headache, only a few hours before admission. She remained in the hospital for twenty-four hours before her exitus. However, the patient of Case 8 had a history of previous eclampsia and the symptoms of toxemia for at least one month; her stay in the hospital was two days. Likewise, Case 19 had had symptoms for four months before admission. Therefore, it appears that we cannot correlate the absence of hepatic lesions with a short duration of symptoms. Apparently other factors enter into the production of the necrosis.

The nature of these focal hyaline or fibrinoid lesions is of considerable interest. They are characteristically small in size and approximately fill one high-power microscopic field under 440X magnification. Adjacent hepatic cells usually involving three to five cords or more in a periportal area lose their distinct cellular outline and take on a brighter and lighter hue with the eosin. Their nuclei have disappeared, and the cell borders seem to run together without a definite line of demarcation. There may or may not be hemorrhage in the immediately surrounding area. The amount of hemorrhage has not been very impressive in these cases, although it is frequently found beneath the liver capsule without any apparent associated hyaline necrosis. When it does occur deep in the liver substance, it is usually extensive and macroscopically visible.

Many of the lesions fail to evoke an inflammatory reaction. Often, however, these necroses result in the appearance of polymorphonuclear leucocytes at their periphery. Case 30 demonstrates widespread focal fibrinoid necrosis with an accompanying acute inflammatory reaction. Likewise, Case 28 and Case 24 show

TABLE VII. ANALYSIS OF STAGES OF RENAL DAMAGE

| | STAGE | | |
|------------------------------|-------|------|------|
| | 1 | 2 | 3 |
| Total Cases: | 11 | 16 | 6 |
| Primiparas | 9 | 8 | 0 |
| Multiparas | 2 | 8 | 6 |
| No previous toxemia | 1 | 2 | 2(?) |
| Previous toxemia | 1 | 6 | 4 |
| Pre-eclampsia | 0 | 4 | 2 |
| Eclampsia | 1 | 2 | 2 |
| Average in years | 19.3 | 25.2 | 30.8 |
| Duration of symptoms in days | 26.6 | 25.3 | 28.4 |

portance.¹⁰ This suggests certainly that the hypertension occurs before any anatomic alteration of the vascular system is visible, and that these arteriolar changes are secondary to the hypertension. This is substantiated by the observation of the lesions in Stage 1.

Finally, it must be remembered that all of these cases are fatal, and the fact that the renal lesions have progressed only to Stage 1 does not preclude a fatal outcome.

Adrenals.—The lesions found in the adrenal glands have been a source of great interest and investigation. Essentially they consist of necrosis and hemorrhage of varying degrees. The knowledge that this damage occurs in eclampsia is not new; indeed, it is described by Dexter and Weiss³ in conjunction with a case report of fatal cortical necrosis of the kidneys occurring in eclampsia. Other authors have reported it as an incidental finding in cases of fatal toxemia.¹³ However, considerably more attention should be devoted to this lesion.

Eleven (33 per cent) of these patients showed this pathologic change in the adrenal glands. Of these, 45 per cent were classified as severe in that practically no functional adrenal cortical tissue remained. The other 55 per cent showed involvement of approximately half of the cortical tissue. There were no cases with minimal lesions. The distribution of the cases is shown in Table VIII.

TABLE VIII. DEGREE OF ADRENAL DAMAGE

| CASE NUMBER | DEGREE |
|-------------|----------|
| 1 | Moderate |
| 4 | Severe |
| 13 | Moderate |
| 18 | Severe |
| 20 | Moderate |
| 21 | Moderate |
| 23 | Moderate |
| 24 | Severe |
| 27 | Moderate |
| 29 | Severe |
| 32 | Severe |

However, examination of the clinical histories of these patients lends new significance to the appearance of this lesion. Initially, attention should be directed to a point strongly emphasized by Dexter and Weiss, namely, that normal blood pressure in toxemic patients does not preclude the presence of shock. They maintain that, after a marked hypertension, a reduction to normal levels, and not below, may be coincident with the existence of the shock syndrome.

A review of the cases in this series presenting severe damage to the adrenals reveals that all are primiparas except Case 32. We can offer no explanation for this. Case 4 expired undelivered twenty-four hours after ad-

All of the changes described above are qualitative in nature and represent progressions of the same underlying pathologic process. To our knowledge no one has attempted to estimate these lesions quantitatively. Therefore, since it appeared to us that the renal changes fall into three general groups, we have established three stages which we think represent progressive degrees of kidney damage in eclampsia.

Stage 1 represents the earliest level of renal damage. It is characterized by the presence of usually avascular glomeruli with an increase in the glomerular nuclei. There is usually moderate thickening of the capillary basement membrane. In this stage there is *no* thickening of the arteriolar wall. Of these 33 fatal cases, 11 fall into this group.

TABLE VI. STAGES OF RENAL LESIONS IN ECLAMPSIA

| | |
|----------|---|
| Stage 1: | a. Avascular glomeruli (\pm) b. Increase in glomerular nuclei c. No visible change in arterioles d. Moderate thickening of basement membrane (\pm) |
| Stage 2: | a. Avascular glomeruli (\pm) b. Increase in glomerular nuclei c. Arteriolar thickening d. Marked thickening of basement membrane e. Fibrinoid changes in glomeruli and arterioles (\pm) |
| Stage 3: | a. Scattered obliterated hyalinized glomeruli b. Fibrosis beneath Bowman's capsule (\pm) c. Generalized arteriolosclerosis d. Kidney of arteriolonephrosclerosis |

The essential difference between Stages 1 and 2 is the finding in the latter group of thickening of the arteriolar wall. It has been suggested that this early change may be attributable to edema. There may or may not be fibrinoid changes in the glomeruli. If the fibrinoid changes are evident in the glomeruli, there is usually an involvement of the arteriole, as well. Sixteen of our cases are in this group.

Stage 3 represents the development of lesions remarkably similar to those of nephrosclerosis. There is a diffuse arteriolo- and arteriosclerosis. There are scattered obliterated, hyalinized glomeruli. Occasionally one sees fibrosis beneath Bowman's capsule. Six of these cases are in Stage 3.

In Table VI are listed the criteria for the foregoing classification.

The results of the analysis of the cases in each stage are shown in Table VII. It will be seen that the percentage of primiparous patients drops from 82 per cent in Stage 1 to 50 per cent in Stage 2, and to 0 in Stage 3, while the proportion of multiparas rises from 18 per cent to 50 per cent, then to 100 per cent. Likewise, with one exception (Case 8), the multiparous patients with a history of preceding toxemia are confined to Stages 2 and 3. The average age for each group rises from 19.3 years to 25.2, to 30.8 in the progressive stages of renal injury. The average duration of symptoms in all stages is practically the same: 26.6, 25.3, and 28.4 days.

Although there are reports to the contrary,^{15, 16} it is generally agreed that the permanent vascular and renal lesion residual of eclampsia and pre-eclamptic toxemia is not glomerulonephritis, but arteriolonephrosclerosis. Dexter and Weiss³ remark that the post-toxic hypertension does not differ from the syndrome of benign or malignant nephrosclerosis. Likewise, the histologic picture is that of benign or malignant nephrosclerosis. Similar observations have been reported by Herrick and Tillman.¹⁴

It has been shown by Reid and Teel^{17, 18} that hypertension residual to toxemia is largely dependent upon the duration of the toxemia. It also appears that the degree of hypertension during the toxemia is another factor of im-

mission, apparently of pulmonary edema that failed to respond to therapy. Case 18 expired in coma eight days after admission and six days after the delivery of a macerated fetus. At the time of death she had a rising NPN and gross hematuria. Case 24 delivered a living child four days after admission and expired six days later. The signs of toxemia were rapidly diminishing in this patient; albuminuria, hematuria, and casts were decreasing. Case 29 delivered on the fifth hospital day; the blood pressure dropped from 300/116 to 90/70 during a three-hour period, and the patient apparently died in shock. Case 32 had a rise in pulse rate and temperature on the fourth hospital day, together with a sudden drop in blood pressure from 270/170 to 120/0, followed shortly by death.

A review of the patients with adrenal lesions of moderate degree reveals that four of the six are multiparas. Case 1 is a patient who died in shock several hours post partum. However, there was focal necrosis of the myocardium with a complete heart-block, as revealed by the electrocardiogram. Since the patient complained of angina, the hypotension was probably cardiac in origin. Case 13 delivered a stillborn fetus on the second hospital day and stopped breathing soon after delivery, the blood pressure being unobtainable. Case 20 delivered a live baby on the second hospital day, remained in deepening coma, and expired two days later. In these adrenals the necrosis is early but extremely widespread. Case 21 delivered a stillborn fetus on the second hospital day and expired in coma and questionable shock fifteen hours later. Case 23 delivered a macerated fetus on the seventh hospital day, developed shock (BP 100/60) unrelieved by blood and plasma, and expired twenty-four hours later. Case 27 delivered on the fifth hospital day, the blood pressure dropped from 300/180 to 90/70 over a period of hours, and the patient expired in shock.

The remaining cases, in whom no adrenal damage is evident, are examined for the shock-like picture. Only two need be considered. Case 7 developed shock postpartum, responded to intravenous fluids, and then developed pulmonary edema, which failed to respond to the usual therapy. Case 17 had hysterotomy and developed shock four days later, which was successfully treated with fluids. This patient probably died of pneumonia and myocarditis.

In summarizing the adrenal changes, it appears that there is a possible relationship between the adrenal damage and the terminal appearance of the shocklike syndrome. In the light of the many widespread lesions in other viscera, it would be gross misinterpretation to say that the sole cause of death was adrenal insufficiency. However, it does appear that adrenal insufficiency secondary to recent widespread injury may be a contributing factor in the exitus of certain patients. A similar mechanism is already known to exist in meningococcemia, resulting in the Waterhouse-Friderichsen syndrome.²⁵⁻²⁷ We do know that hypertensive and toxemic patients tend to show a marked drop in blood pressure after delivery.²⁰⁻²⁴ If sufficient adrenal damage were to exist in such a patient, she might tolerate that hypotension very poorly and fail to respond.

Additional Lesions.—Pathologic changes in the other viscera will be discussed under a combined heading and are demonstrated in Chart 7.

The lungs showed pneumonia of varying degrees in 16 of the cases. These infections were usually marked by pulmonary edema which failed to respond to the usual therapy. An associated purulent bronchitis was present in four of these cases.

Of considerable clinical interest was the presence of unrecognized bilateral hydrothorax: Case 13, 550 c.c. and 450 c.c.; Case 16, 1,000 c.c. and 1,000 c.c.; Case 19, 500 c.c. and 500 c.c.; Case 27, 300 c.c. and 200 c.c.; Case 28, 700 c.c. and 450 c.c. Whether the removal of such fluid would have altered the outcome is highly debatable.

TABLE XI. SUMMARY OF PATHOLOGIC FINDINGS

| CASE | HEART | | | | BRAIN | | FOCAL NECROSIS OF LIVER | FOCAL NECROSIS PAN- CREAS | STAGE OF RENAL LESION | ADRENAL AND HEM- ORRHAGE | PNEU- MONIA | PUL- MONARY EDEMA | HYDRO- THORAX | ENDO- METRI- TIS | CYSTITIS |
|-------|---------------|-----------------|-----------------------|------------------------|---------------|-----------------|----------------------------------|------------------------------------|--------------------------------|--------------------------------|----------------|-------------------------|------------------|------------------------|----------|
| | NECRO- SIS | HEMOR- RHAGE | MYO- CARDI- TIS | ENDO- CARDI- TIS | NECRO- SIS | HEMOR- RHAGE | ARTER- ITIS | | | | | | | | |
| 1 | + | + | | | + | | | | 2 | + | + | | | | |
| 2 | | | | | | | | | 2 | | | + | | | |
| 3 | | | | | + | | | | 1 | | | + | | | |
| 4 | | + | | | + | | | | 1 | + | + | + | | + | |
| 5 | + | + | | | + | | | | 1 | | + | + | | | |
| 6 | | | | | + | | | | 2 | | + | + | | | |
| 7 | | + | | | + | | | | 2 | | + | | | | |
| 8 | | + | | | | | | | 1 | | | + | | + | |
| 9 | | + | | + | + | | | | 1 | | + | | | + | |
| 10 | | | | | + | | | | 2 | | | | | + | |
| 11 | | | | | + | | + | + | 1 | | | | | + | |
| 12 | | | | | + | | + | + | 3 | | + | | | | + |
| 13 | | + | | | + | | | | 1 | + | + | + | + | | |
| 14 | | + | | | + | | | | 2 | | + | | | + | |
| 15 | | | | | + | | | | 3 | | | | | + | |
| 16 | | | | | + | | | | 2 | | + | + | | | |
| 17 | + | | + | | + | | | | 3 | | + | | | | |
| 18 | | | | | + | | | | 1 | + | + | + | | | + |
| 19 | | | | | | | | | 1 | | | + | + | | |
| 20 | | | | | + | | | | 2 | + | | + | | + | |
| 21 | | | | | + | | | | 2 | + | | | | | |
| 22 | | | | | + | | | | 2 | | + | | | | |
| 23 | | | + | | + | | | | 2 | + | | + | | + | |
| 24 | | | | | + | | | | 2 | + | | | | + | |
| 25 | + | | | | + | | + | | 2 | | + | | | | |
| 26 | | | | | + | | + | | 3 | | | + | | | + |
| 27 | | + | | | + | | | | 2 | + | | + | + | | |
| 28 | | | | | + | | | + | 1 | | | | + | | |
| 29 | | | | | + | | | | 1 | + | | | | | |
| 30 | | + | | | + | | + | + | 2 | | + | + | | | |
| 31 | | + | | | + | | + | | 2 | | + | + | | | |
| 32 | | + | | | + | | | | 3 | + | + | | | | |
| 33 | | | | | + | | | | 3 | | | | | + | |
| Total | 4 | 12 | 2 | 1 | 1 | 3 | 4 | 4 | | 11 | 16 | 16 | 5 | 10 | 5 |

such significance that it may cause the death of the patient. This is excellently demonstrated by the massive cerebral hemorrhage from necrosis of the cerebral arteries, the myocardial necrosis which led to heart failure, and the massive destruction of the adrenals which, if it did not lead to vascular collapse, probably prevented recovery from that collapse.

However, these lesions are significant aside from their immediate effects. They reflect tissue changes resulting from altered physiology of the vascular system. In the light of recent reports, the nature of the altered vascular function is considerably clarified.

The underlying mechanism of visceral damage depends upon a generalized vasoconstriction.^{3, 29} This is manifested by the retinal arterioles in the toxemic patient.^{30, 31} Indeed, the progress of the toxemia can be measured by daily examination of these arterioles to determine whether the vascular spasm persists, becomes more accentuated, or is lessening.³² It has also been observed in the retina that, if the vascular spasm persists, in a certain percentage of cases profound and permanent changes take place in the arterioles.³⁰

Hertig³³ believes that the essential lesion exists in the precapillary arteriole and that the nature of this change is an arteriolitis. We agree that such changes can and do take place. However, it must be remembered that Goldblatt³⁴ in 1938 demonstrated that arterial and arteriolar changes of a comparable nature could be produced merely by the presence of hypertension. Similar results have been reported by Wilson and Byrom,^{35, 36} who also found focal necrosis in the heart, pancreas, and liver as associated changes. Petechial hemorrhages were characteristic of these vascular lesions.

Therefore, it seems reasonable to postulate, as Dexter and Weiss have suggested, the following sequence of events: a vasoconstriction occurs with a resulting hypertension, which leads to small arterial and arteriolar changes; these vascular changes, together with local tissue hypoxia, result in the petechial hemorrhages and the focal necroses. The lack of change in the precapillary arterioles in our Stage 1 of the renal lesion is in accord with this hypothesis.

It may be profitable to examine these lesions in the light of certain recent observations relating to the possible mechanisms involved in the etiology of eclampsia to see if there is any correlation between the various hypotheses suggested and the anatomical changes observed. For example, Smith and Smith in a number of reports have created a most interesting hypothesis. They have isolated a euglobulin toxic factor from the menstrual flow^{37, 38} and consider it to be the agent responsible for the arteriolar and endometrial changes in menstruation. A similar substance³⁹ has been isolated from pleural exudate by Menkin.³⁹ To this he has given the name "necrosin." Smith and Smith postulate that the senile changes which take place in the placenta⁴² (perhaps on the basis of inadequate blood supply) result in the production of "necrosin." This in turn acts upon the vascular system of the mother. They also suggest that "necrosin" may come from any source of tissue destruction.

This seems compatible with the concept that foci of infection may play some role in the etiology of eclampsia;^{43, 44} such foci would provide an extrauterine source of "necrosin." Evidence in favor of this is demonstrated in Case 28, in

Acute endometritis was present in ten cases. This is probably of significance only in those cases which developed septicemia.

The heart was the site of hemorrhage in twelve patients. Four of these showed focal necrosis of the myocardium with slight cellular reaction. There were two cases of myocarditis, one characterized by the focal aggregation of polymorphonuclear leucocytes, and the other by a diffuse scattering of round cells. There was one case of focal acute endocarditis. Idiopathic focal necrosis of the myocardium has been described²⁸ as occurring in normally pregnant women, but we can see no similarity between the reported lesion and those of our own cases.

The pancreas demonstrated focal necrosis in four cases. We consider this to be of no particular significance, save that it is a manifestation of the underlying mechanism of damage in the pathogenesis of eclampsia.

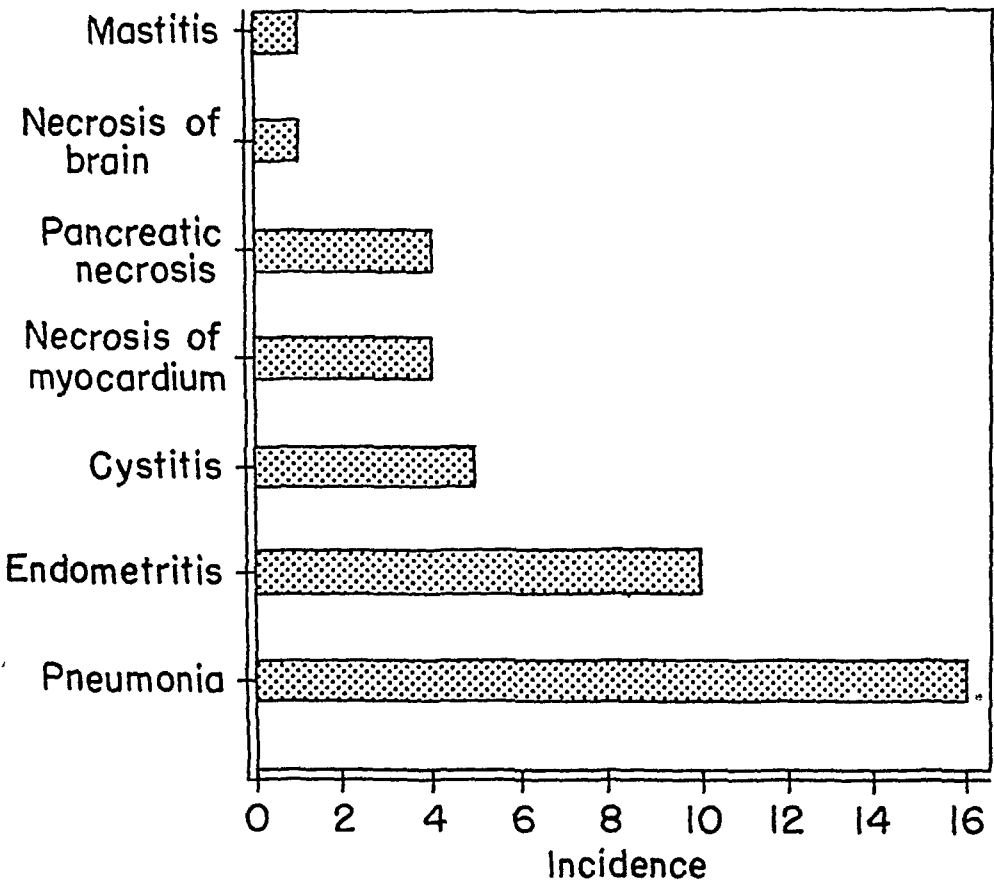


Chart 7.—Additional lesions.

Cystitis was present in five cases.

Acute purulent mastitis was found in one case.

Focal necrosis of the brain was present in one case. Cerebral hemorrhage was also present in three cases. In two (Cases 25 and 31) this hemorrhage was massive. These two cases, as well as Cases 21 and 26, demonstrated cerebral arteritis and arteriolitis with necrosis of the vessel walls.

Discussion

The interpretation of these lesions is a fascinating and highly complex problem. Each visceral change becomes important, not only because it reflects the mechanism of its own production, but because it, too, in turn, may be of

hypertension, found a great increase in positive results when a focus of mixed infection was present.

Another very interesting observation is the fact that the vascular system in toxemic patients is far more sensitive to vasopressor substances than that of normal nonpregnant women, of normally pregnant women, and of puerperal women.⁴⁷⁻⁴⁹ Moreover, it has been shown⁴⁹ that this is an acquired characteristic and appears some time after the seventeenth week of gestation and prior to the onset of symptoms. Other observations by Browne⁴⁹ suggest that this vascular sensitization may be caused by excessive amounts of gonadotropin. This also conforms to our concept of hormone imbalance in eclampsia, namely, decreased estrogen and progesterone and a marked increase in gonadotropin.⁵⁰⁻⁵⁶

The role of a pre-existing hypertension in increasing the incidence of toxemia and eclampsia is established, but not at all clear. Certain experimental work by Dill and Erickson⁵⁷ in creating hypertension in pregnant animals resulted in the appearance of lesions similar to those in eclampsia. If it could be demonstrated that hypertension, regardless of its cause, could result in uterine vascular changes which would produce relatively inadequate placental blood supply and, in turn, premature senile placental changes, then the role of pre-existing hypertension would be greatly clarified.

Further discussion of the pathogenesis of eclampsia does not fall within the scope of this study. Suffice it to say that all the lesions described reflect the profoundly altered physiology of the vascular system and, in addition, bear considerable significance in themselves with respect to the life of the patient.

Summary

1. Thirty-three fatal cases of eclampsia examined at autopsy are reviewed.
2. Analysis of the clinical histories has been presented in relation to age, parity, race, prenatal care, family history, previous medical and obstetric history, symptoms, physical findings on admission, duration of pregnancy, blood chemistry, and duration of hospital stay prior to death.
3. Hepatic lesions consist of focal fibrinoid necrosis, usually of recent origin, with or without hemorrhage.
4. Renal lesions have been divided into three stages which represent steps in the development of permanent renal change: Stage 1, with glomerular but no arteriolar alterations, was typical in 33 per cent of the cases; Stage 2, characterized by thickening of the arteriolar wall, was observed in 48 per cent of the cases; Stage 3, with lesions similar to arteriolonephrosclerosis, characterized 18 per cent of the cases.
5. Eleven cases demonstrated hemorrhage and necrosis in the adrenals, five of which were classified as severe. An attempt has been made to correlate these lesions with vascular collapse prior to death.
6. Additional lesions found were: pneumonia; focal necrosis of the myocardium, pancreas, and brain; acute endometritis; cerebral hemorrhage; cystitis; acute mastitis; and cerebral arteritis and arteriolitis.
7. An attempt is made to correlate the observed lesions with some current hypotheses concerning the pathogenesis of eclampsia.

which the patient had careful and frequent prenatal care. In this case the development of an acute purulent mastitis resulted in the explosive onset of eclampsia with death thirty-six hours after the first symptom. The role of infection in producing liver necrosis has been well demonstrated by Seely.⁴⁵ Likewise, Smith and Zeek,⁴⁶ in producing periarteritis nodosa by rapidly rising

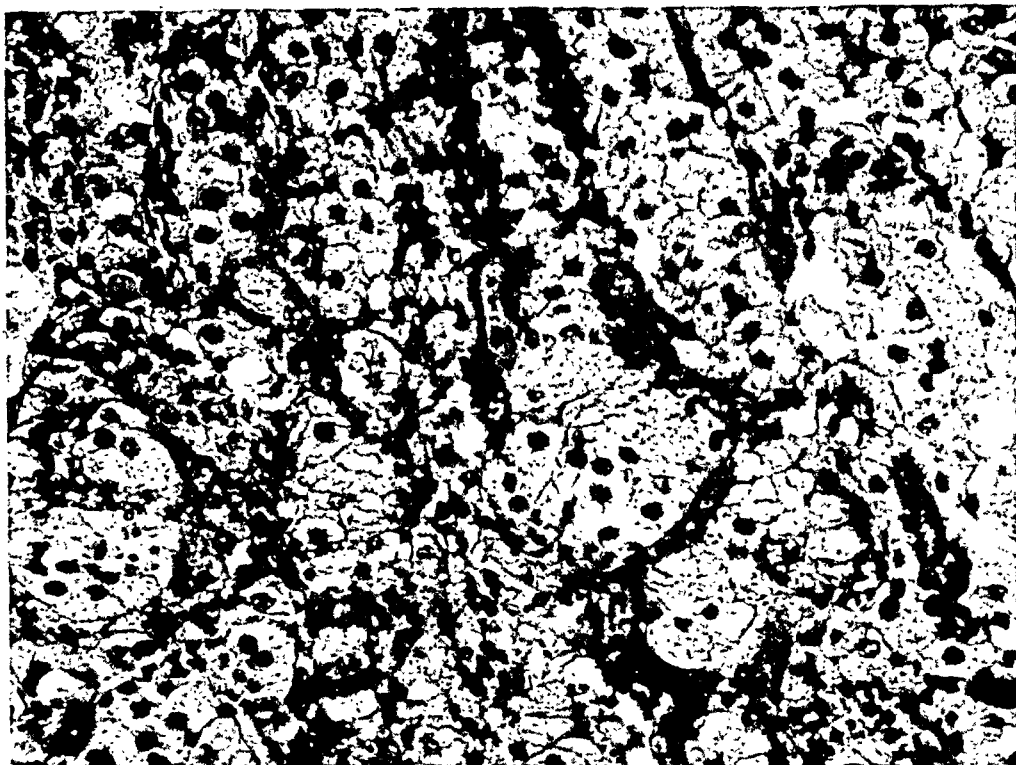


Fig. 1.—Capillary necrosis in the adrenal gland: Case 20—The photograph shows the mechanism of adrenal damage in eclampsia. The capillaries between the fascicles have undergone fibrinoid necrosis. Other areas in this gland demonstrated progression of this lesion, namely, parenchymal necrosis and hemorrhage. ($\times 440$)

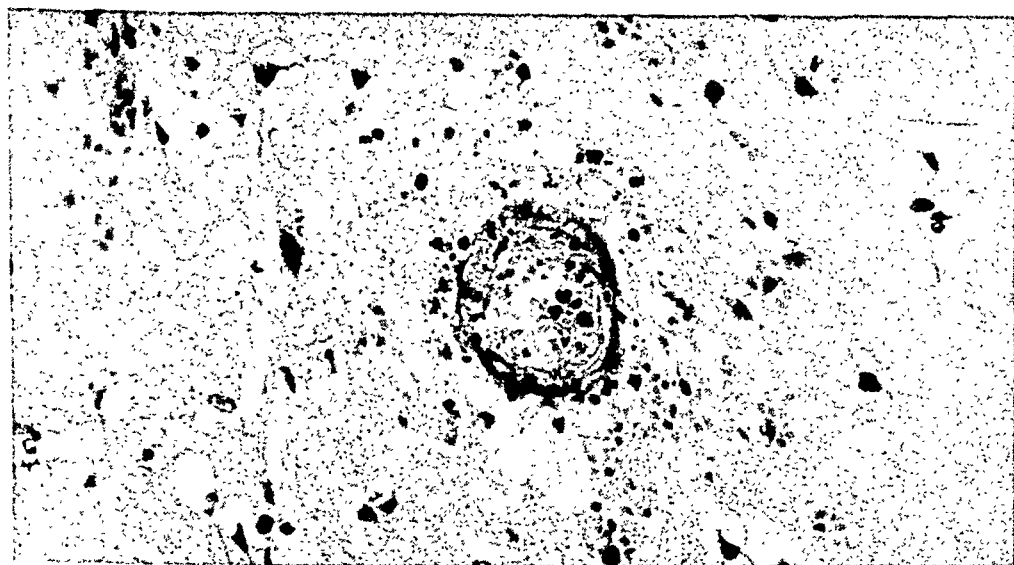


Fig. 2.—Cerebral vascular changes in eclampsia: Case 25—The photograph shows edema and necrosis of the vessel wall. Polymorphonuclear leukocytes are evident both in the perivascular space and in the wall itself. Scattered erythrocytes are present in the surrounding brain tissue. ($\times 440$)

ELEVATED BLOOD PRESSURE IN PREGNANCY*

A Report of 1,800 Cases

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DURING the full term of gestation, the physiologic processes of the human female are placed under a severe strain of added work. Fortunately, the structures of the body are endowed with sufficient margins of safety to allow the normal woman to bear her children without resultant permanent damage to her mental and physiologic well-being. However, for the woman suffering from disease processes, either functional or organic, or for the woman whose body functions can operate safely only at normal capacity, pregnancy becomes a burden that temporarily or permanently impairs the health of the prospective mother. Of the medical problems that complicate normal pregnancy, those associated with elevated blood pressure are probably the most serious because of their relative frequency and severity.

In an attempt to better evaluate cases associated with elevated blood pressure over 140/90, the records of the Lewis Memorial Maternity Hospital were reviewed. For simplicity of study they were divided into four groups: (1) The pre-eclamptic, which included those cases that had normal pressure in their early pregnancy, but as term approached the pressure gradually or suddenly rose over 140/90. We are fully cognizant that this group will not only include the true pre-eclampsies, but also potential hypertensives, that manifest themselves as a result of the added burden of pregnancy, and those cases that are classed by some as low reserve kidney. If we err in including these cases as pre-eclampsies, the error is in the patient's favor since she comes under much closer observation. (2) This is the eclamptic group which requires no further elaboration. (3) This is the group which will be referred to as the nephritis group, exclusive of cases of ascending or pyelonephritis. (4) The fourth and last group is the hypertensive which includes all types, the etiology and classification of which is better discussed in texts of internal medicine.

Material

From 1931 to 1945, inclusive, 28,263 mothers were delivered at the Lewis Memorial Maternity Hospital. Of these, 1,800 patients, or 6.36 per cent, had a blood pressure of, or over, 140/90 during all or part of their pregnancy. Table I represents the yearly incidence of this complication. The first and last line of the table is the total for the fifteen-year period which was reviewed. Pre-eclampsia represented 1,454 cases, or 5.14 per cent; eclampsia, 51 cases, or 0.18 per cent; nephritis, 12 cases, or 0.04 per cent; and hypertension, 283 cases,

*Read at a meeting of the Chicago Gynecological Society, Jan. 17, 1947.

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years varied from 27 to 28 years in all groups except the hypertensive, which averaged 32.3 years. The average normal "weight" varied from 127 pounds to 137 pounds, except for the hypertensive who averaged 152 pounds. The fourth line in Table III shows the "gain in weight" up to the period of gestation at which the pressure became elevated, and is 26 pounds and 27.4 pounds for the pre-eclamptic and eclamptic groups, respectively. This represents the minimum weight gained by these patients, since many of them disregarded or refused treatment, and thus gained an additional 10 to 20 pounds during the remaining weeks of their pregnancy.

Cardinal Symptoms and Physical Findings.—In the pre-eclamptic group 18.9 per cent complained of headaches, 31.1 per cent of ankle edema, 5.9 per cent of epigastric pain, 10.7 per cent of visual disturbances, and albuminuria of varying degree was found in 67.2 per cent. These findings were markedly

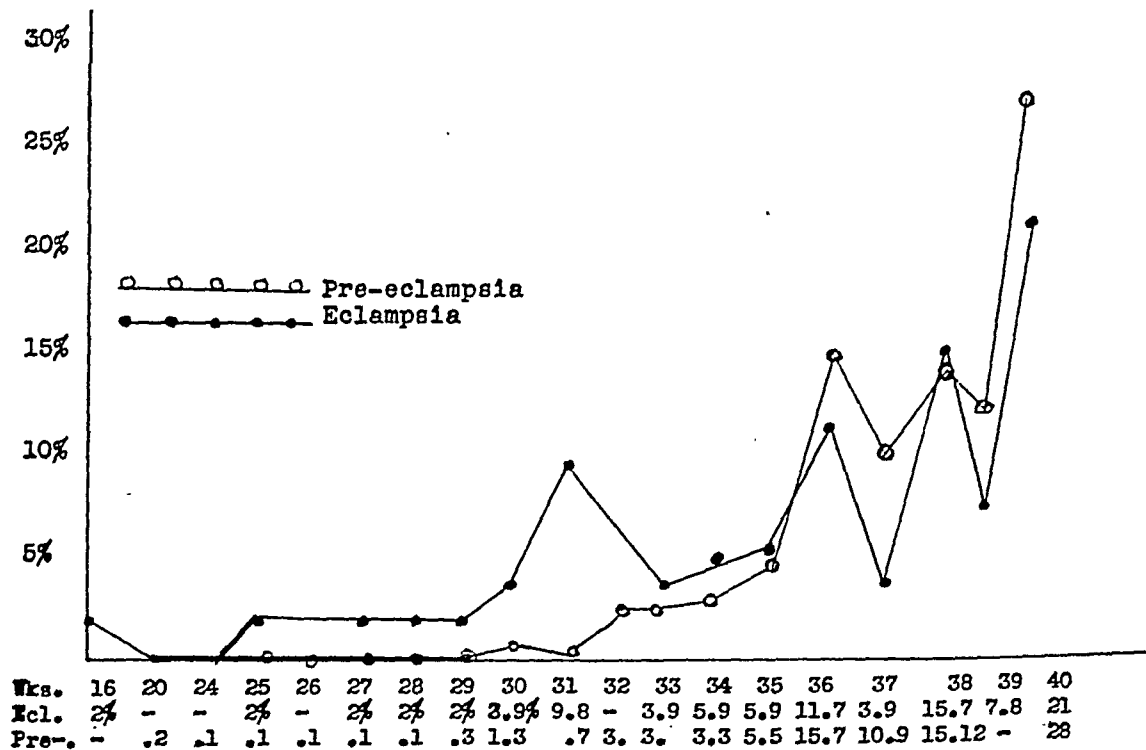


Fig. 1.—Week of appearance of elevated blood pressure.

TABLE III

| | PRE-ECLAMPSIA | | ECLAMPSIA | | | | HYPER-TENSIVE | |
|---|---------------|----------|-----------|----------|---------|----------|---------------|----------|
| | NUM-BER | PER CENT | NUM-BER | PER CENT | NUM-BER | PER CENT | NUM-BER | PER CENT |
| Height, inches | 1154 | 63.4 | 45 | 63.6 | 12 | 62.5 | 250 | 63.4 |
| Age, years | 1450 | 27.8 | 51 | 27.2 | 12 | 27.6 | 281 | 32.3 |
| Normal weight, lbs. | 1303 | 137.5 | 41 | 127.9 | 11 | 132.8 | 265 | 152.2 |
| Weight gain to onset of elevation of blood pressure | 1295 | 26.0 | 41 | 27.4 | ----- | | ----- | |
| Headaches | 275 | 18.9 | 36 | 72.0 | 9 | 75.0 | 61 | 21.6 |
| Ankle edema | 452 | 31.1 | 35 | 70.0 | 9 | 75.0 | 84 | 29.6 |
| Epigastric pain | 85 | 5.9 | 16 | 32.0 | 2 | 16.6 | 7 | 2.5 |
| Visual disturbances | 156 | 10.7 | 23 | 46.0 | 7 | 58.3 | 26 | 9.1 |
| Albuminuria | 930 | 67.2 | 49 | 98.0 | 12 | 100.0 | 160 | 58.8 |
| Vertigo | - | - | - | - | - | - | 14 | 4.9 |
| Casts (average) | ? | | ? | | 12 | 100.0 | ? | |

or 1.0 per cent. The last column on the right side of the table is the percentage of pre-eclampsies that progressed into eclampsia. This incidence was 3.4 per cent. However, it is possible also for either the nephritic or the hypertensive to develop eclampsia.

TABLE I. INCIDENCE BY YEARS OF ELEVATED BLOOD PRESSURE 140/90

| TOTAL CASES | PRE-ECLAMPSIA | | ECLAMPSIA | | NEPHRITIS | | HYPERTENSIVE | | TOTAL | E P & E |
|---------------|---------------|----------|-----------|----------|-----------|----------|--------------|----------|----------|------------|
| | NUM-BER | PER CENT | NUM-BER | PER CENT | NUM-BER | PER CENT | NUM-BER | PER CENT | PER CENT | PER CENT |
| 1931-45 28263 | 1454 | 5.14 | 51 | 0.18 | 12 | 0.04 | 283 | 1.00 | 6.36 | 3.4 |
| 1931 1620 | 21 | 1.29 | 2 | 0.12 | 0 | - | 1 | 0.07 | 1.48 | 8.7 |
| 1932 2321 | 137 | 5.90 | 3 | 0.13 | 2 | 0.09 | 13 | 0.56 | 6.68 | 2.1 |
| 1933 2145 | 157 | 7.33 | 3 | 0.14 | 1 | 0.04 | 36 | 1.67 | 9.18 | 1.3 |
| 1934 2236 | 228 | 10.20 | 4 | 0.17 | 1 | 0.05 | 31 | 1.38 | 11.80 | 1.3 |
| 1935 2103 | 101 | 4.80 | 7 | 0.33 | 1 | 0.04 | 27 | 1.28 | 6.46 | 6.5 |
| 1936 2139 | 77 | 3.64 | 6 | 0.28 | 1 | 0.06 | 24 | 1.12 | 5.10 | 7.2 |
| 1937 2097 | 45 | 2.14 | 6 | 0.28 | - | - | 8 | 0.38 | 2.80 | 11.8 |
| 1938 2087 | 144 | 6.89 | 5 | 0.30 | - | - | 39 | 1.87 | 9.06 | 3.3 |
| 1939 1911 | 116 | 6.07 | 1 | 0.06 | 2 | 0.10 | 40 | 2.09 | 8.32 | 0.9 |
| 1940 1849 | 82 | 4.43 | 4 | 0.22 | 3 | 0.16 | 10 | 0.54 | 5.35 | 4.6 |
| 1941 1806 | 113 | 6.27 | 4 | 0.22 | - | - | 15 | 0.81 | 7.30 | 3.4 |
| 1942 1902 | 79 | 4.15 | 3 | 0.16 | 1 | 0.05 | 19 | 1.00 | 5.36 | 2.7 |
| 1943 1850 | 81 | 4.37 | 2 | 1.11 | - | - | 7 | 0.38 | 4.86 | 2.4 |
| 1944 1218 | 42 | 3.44 | 1 | 0.09 | - | - | 10 | 0.81 | 4.34 | 2.3 |
| 1945 979 | 31 | 3.16 | - | - | - | - | 3 | 0.31 | 3.47 | 0.0 |
| Total 28263 | 1454 | 5.14 | 51 | 0.18 | 12 | 0.04 | 283 | 1.00 | 6.36 | 3.4 |

Parity.—Table II represents the parity of the 1,800 cases expressed in percentages. The pre-eclamptic group was made up of 52 per cent primiparas and 48 per cent multiparas; the eclamptic group was 80 /per cent primiparas and 20 per cent multiparas; the nephritis group was 50 per cent and 50 per cent; and the hypertensive group was 25 per cent primiparas and 75 per cent multiparas.

TABLE II. PARITY

| | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|------------------------------|------|------|------|------|------|-----|-----|-----|-----|-----|-----|
| Pre-eclampsia 1,454 cases | 52.3 | 18.5 | 12.6 | 6.8 | 4.2 | 1.9 | 1.6 | 1.2 | 0.5 | 0.2 | 0.2 |
| Eclampsia 51 cases | 80.3 | 5.8 | 3.9 | 5.8 | 1.9 | | | | | | |
| Nephritis 12 cases | 50.0 | 33.3 | 8.3 | 8.3 | | | | | | | |
| Hypertension 283 cases | 25.4 | 18.6 | 12.5 | 11.1 | 10.3 | 5.4 | 6.8 | 3.2 | 1.8 | 2.1 | 2.9 |

Figures represent percentages of total. 1,800 cases, 1931 to 1945 inclusive.

Time of Elevation of Blood Pressure.—Fig. 1 is a graphic representation of the period of gestation in weeks, when the pressure became elevated in the pre-eclamptic and eclamptic groups. The former is represented by the line with open circles, and the latter by the continuous line. Suffice it to say that 90 per cent of each group first demonstrated the elevation of pressure after the thirtieth week of gestation, and the incidence rapidly rose as term approached. The week of gestation was determined by the date of the last menstrual period, and is accurate for the greatest majority. The margin of error would be a plus or minus two to four weeks.

Physical Characteristics.—The average "height" of each group was almost identical, and varied from 62.5 inches to 63.6 inches. The average "age" in

cent of the eclamptic group. The absence of elevated blood pressure in 6 per cent of the latter may be explained on the basis of postpartum convulsions. Duration of the first and second stages of labor in primiparas varied from thirteen to sixteen hours. The nephritis group averaged only 5.1 hours; but since only three cases were averaged, this figure may be disregarded.

TABLE V

| | PRE-ECLAMPSIA | | ECLAMPSIA | | NEPHRITIS | | HYPERTENSIVE | |
|----------------------------------|---------------|-----------|--------------|-----------|-------------|----------|--------------|--------------|
| | NUM-BER | PER CENT | NUM-BER | PER CENT | NUM-BER | PER CENT | NUM-BER | PER CENT |
| Elevated blood pressure at labor | 1317 | 91.6 | 47 | 94.0 | 12 | 100.0 | 283 | 100.0 |
| Labor in primipara in hours | 717 | 16.1 | 30 | 13.4 | 3 | 5.1 | 65 | 14.3 |
| Labor: Spontaneous | 1358 | 95.1 | 32 | 82.0 | 8 | 80.0 | 263 | 93.9 |
| Induced | 70 | 4.9 | 7 | 18.0 | 2 | 20.0 | 17 | 6.1 |
| Castor oil and quinine | 46 | 65.7 | 3 | 42.8 | 1 | 50.0 | 5 | 29.4 |
| Ruptured membranes | 9 | 12.8 | 1 | 14.3 | - | - | 5 | 29.4 |
| Bag | 11 | 15.7 | 3 | 42.8 | 1 | 50.0 | 7 | 41.2 |
| Bougie | 4 | 5.8 | - | - | - | - | - | - |
| Gestation: 40 or more weeks | 1138 | 78.2 | 20 | 39.2 | 6 | 50.0 | 183 | 64.6 |
| Gestation: Less than 40 weeks | 316 5 N.V. | 21.8 - | 31 1 N.V. | 60.8 - | 6 1 N.V. | 50.0 | 91V 9N.V. | 32.2* 3.2 |
| Delivery: ‡ Spontaneous | 1155 | 77.4 | 24 | 43.6 | 8 | 66.7 | 247 | 89.2 |
| Operative | 339 | 22.6 | 31 | 56.4 | 4 | 33.3 | 30 | 10.8 |

*These figures represent percentages of cases of induced labor.

†V represents cases of sufficient gestation for viability.

‡This is for infants delivered, *not* mothers.

Onset of labor was spontaneous in 95 per cent of the pre-eclamptics, 82 per cent of the eclamptics, 80 per cent of the nephritics, and 94 per cent of the hypertensives. The different methods of induction are enumerated. Castor oil and quinine method was efficacious only if the cervix was effaced and the uterus ready to begin labor. Stripping and rupturing the membranes was much more efficient in inducing labor when the cervix was effaced and the uterus irritable. The employment of bags is not as frequently used as in former years, but it is felt that it still has its place in certain cases. The bougie as a method of inducing labor was used in four cases during the first few years that the hospital was opened. It has not been used since that time.

Length of Gestation.—Forty or more weeks of gestation was reached by 78 per cent of the pre-eclamptics, 39 per cent of the eclamptics, 50 per cent of the nephritics, and 65 per cent of the hypertensive cases. Of those patients who did not reach forty weeks of gestation, there were five pre-eclamptics, one eclamptic, one nephritic, and nine hypertensives that did not reach thirty weeks. All of the infants born of this latter group were stillborn, and all but one weighed less than 1,000 grams.

Delivery.—This was by spontaneous means in 77 per cent of the infants born of pre-eclamptic mothers, 44 per cent of the infants in the eclamptic group, 67 per cent of the infants in the nephritis group, and 89 per cent of the infants in the hypertensive group. The different types of operative delivery will be mentioned later.

Size of the Infants.—(Table VI.) The average weight of the infants in each group was 3,277 Gm. in the pre-eclamptic, 2,781 Gm. in the eclamptic, 2,860

elevated in the eclamptic group which showed headaches in 72 per cent, ankle edema in 70 per cent, epigastric pain in 32 per cent, visual disturbances 46 per cent, and albuminuria in 98 per cent. Had the urine specimen been obtained at the proper time, probably all cases of postpartum eclampsia would have demonstrated albuminuria. In the nephritic group, 75 per cent complained of headaches, 75 per cent of ankle edema, 16.6 per cent of epigastric pain, 58.3 per cent of visual disturbances, and 100 per cent had albuminuria and casts. In the hypertensive group headaches were present in 21.6 per cent, ankle edema in 29.6 per cent, epigastric pain in 2.5 per cent, visual disturbances in 9.1 per cent, albuminuria in 58.8 per cent, and vertigo in 4.9 per cent.

Treatment.—The first line of Table IV represents the percentage of patients in this series admitted to the hospital before labor, and their average stay in days before labor began. The remainder of Table IV is a summary of the treatment used over the fifteen-year period. The percentages for magnesium sulfate include both the saturated solution given as a saline cathartic and the concentrated solution given parenterally, even though the action is different. Our present treatment may be summarized as follows:

TABLE IV

| TREATMENT | PRE-ECLAMPSIA | | ECLAMPSIA | | NEPHRITIS | | HYPERTENSIVE | |
|----------------------------|---------------|----------|-----------|----------|-----------|----------|--------------|----------|
| | NUM-BER | PER CENT | NUM-BER | PER CENT | NUM-BER | PER CENT | NUM-BER | PER CENT |
| Patients admitted hospital | | | | | | | | |
| average number days | 4.75 | 30.1 | 7.7 | 50.9 | 20.3 | 66.6 | 6.7 | 30.7 |
| Ammonium chloride | 108 | 7.4 | 2 | 3.9 | 0 | 0 | 14 | 4.9 |
| Sedation | 551 | 37.9 | 38 | 74.5 | 10 | 83.3 | 132 | 46.6 |
| Magnesium sulfate | 288 | 19.8 | 33 | 64.7 | 5 | 41.6 | 180 | 63.6 |
| Hypertonic fluids | 37 | 2.5 | 25 | 49.0 | ----- | | 12 | 4.2 |
| Diet: L.P.S.F. | 661 | 45.5 | 36 | 70.5 | 7 | 58.3 | 166 | 58.6 |
| H.P.S.F. | 48 | 3.3 | - | - | - | - | - | - |
| N.P.S.F. | 22 | 1.5 | - | - | - | - | - | - |
| Milk | 13 | 0.9 | - | - | - | - | - | - |

1. All normal patients are given a 1,800 calorie diet made up of 85 Gm. of protein, 75 Gm. of fat, and 200 Gm. of carbohydrate. (These figures are obtained from the diet being used at the Chicago Lying-in Clinic.)
2. Institution of a salt free 85 Gm. protein diet, sedation and enteric coated tablets of ammonium chloride in 1½ to 6 Gm. doses daily if the pressure begins to rise and is accompanied by a sudden increase of weight.
3. Absolute bed rest in the hospital if the pressure remains over 140/90.
4. Hypertonic glucose in water, sedation, and parenteral magnesium sulphate therapy are used in amounts commensurate with the severity of the toxemia. For the eclamptic severe medical management is used. If the pregnancy must be terminated because of failure to respond to medical management, and the cervix is in a state not suitable for delivery from below, cesarean section is performed under local anesthesia. In the nephritic and hypertensive patient, the usual medical management is carried out by the internist, and is augmented by rest that varies from slight restriction of household duties to absolute bed rest in the hospital throughout the pregnancy, depending upon the severity of the symptoms. The abbreviations in the last line under the heading of diet indicate low protein, high protein, and normal protein salt free diets.

Labor and Delivery.—(Table V.) Blood pressure was found to be elevated at the time of labor in 91.6 per cent of the pre-eclamptic group, and in 94 per

were done chiefly for delivery of the second twin. Table IX shows some of the other indications for sections. Elderly primiparity is not considered a primary indication. One case of placenta previa, two cases of abruptio, four cases of previous section for disproportion, and nine cases of primary disproportion were sectioned because of these complications, and not because of the associated hypertension. Thus the toxemia was the primary indication for 25 of the 41 patients sectioned.

TABLE VII

| | MATERNAL DEATHS |
|-------------------------------|---|
| Eclampsia | 4 cases |
| Nephritis | 1 case nephritis with edema pneumonia and empyema thyroiditis |
| Pre-eclampsia | 5 cases (a) pulmonary embolism 2 cases (b) ruptured uterus and shock (c) ventricular hemorrhage (d) bowel obstruction, resection, and peritonitis |
| Incidence: 1:2826 | |
| 1931 to 1935, 7 cases, 1:1489 | |
| 1936 to 1940, 2 cases, 1:5041 | |
| 1941 to 1945, 1 case, 1:7755 | |

TABLE VIII. OPERATIVE DELIVERIES

| | PRE-ECLAMPSIA | | ECLAMPSIA | | NEPHRITIS | | HYPERTENSIVE | |
|------------------------|---------------|----------|-----------|----------|-----------|----------|--------------|----------|
| | NUM-BER | PER-CENT | NUM-BER | PER-CENT | NUM-BER | PER-CENT | NUM-BER | PER-CENT |
| Low and prop. forceps | 209 | 61.8 | 9 | 29.0 | 1 | 25.0 | 17 | 56.7 |
| Midforceps | 51 | 15.0 | 5 | 16.0 | - | - | 4 | 13.3 |
| Breech extraction | 31 | 9.2 | 3 | 10.0 | - | - | 6 | 20.0 |
| Version and extraction | 23 | 6.8 | 2 | 7.5 | 1 | 25.0 | - | - |
| Cesarean section | 24 | 7.1 | 12* | 38.0 | 2 | 50.0 | 3 | 10.0 |
| Low cervical | 14 | - | - | - | - | - | - | - |
| Classical | 10 | - | 12 | - | 2 | - | 3 | - |
| Pubiotomy | 1 | 0.2 | - | - | - | - | - | - |
| Total | 339 | | 31 | | 4 | | 30 | |

*One case of posthumous section.

TABLE IX. CESAREAN SECTIONS (41 CASES)

| | | | | | | |
|--------------------|-----------------|----------------------|---------------------|-----------------------|---------------------|------------------------|
| Low cervical 10 | Classical 31 | Eclampsia 12 | Pre-eclampsia 24 | Nephritis 2 | Hyper-tensive 3 | |
| | | Placenta previa 1 | Abruptio 2 | Previous section 4 | Disproportion 13 | Elderly primipara 3 |

Time of convulsions.—Convulsions occurred ante partum in 35 per cent, intra partum 33 per cent, and post partum in 31 per cent of the 51 cases of eclampsia presented.

Discussion

During the fifteen-year period that has been reviewed, the maternal death rate has continued to improve at the Lewis Maternity Hospital. Since some of our deaths were preventable, we are still striving to reach the ideal goal. This

Gm. in the nephritic, and 3,269 Gm. in the hypertensive. The small size of the infant born of the eclamptic and nephritic mother has been observed by nearly all obstetricians.

Stillborn and Neonatal Deaths.—For the pre-eclamptic this incidence was 3.1 per cent and 1.5 per cent; for the eclamptic, 18.1 per cent and 7.2 per cent; for the nephritic, 33.3 per cent and 8.3 per cent; and for the hypertensive 4.7 per cent and 1.4 per cent. A fetal salvage of only seven out of twelve infants born of the nephritic mothers shows the seriousness of this complication as far as the infant is concerned, to say nothing of its injurious effect to the mother.

Twins.—Only in the hypertensive group was the normal ratio of 1:86 pregnancies approximated. In this group the ratio was 1:94. In the pre-eclamptic and eclamptic groups, the incidence was markedly increased being 1:36 for the former and 1:13 for the latter.

Maternal Deaths.—There were five maternal deaths in the pre-eclamptic group for a percentage incidence of 0.34 per cent. Four of the 51 eclamptic mothers died for an incidence of 7.86 per cent. One case or 8.3 per cent of the nephritic mothers died. There were no deaths in the hypertensive group; but five of these 283 cases developed cardiac decompensation, two of which were accompanied by hydrothorax, and one of which was an acute pulmonary edema.

Table VII shows the breakdown of the maternal deaths. By means of early ambulation and other methods that will prevent thrombus formation, it is hoped that the incidence of pulmonary embolism will be lowered. The case of ruptured uterus and shock was one of a transverse presentation that was mismanaged. The case of bowel obstruction and peritonitis can be explained on the basis of trauma to the bowel resulting from some overzealous individual's attempt to express a retained placenta through a closed cervix. The figures at the bottom of Table VII represent the incidence of maternal deaths in cases associated with elevated blood pressure. For the fifteen-year period this was 1:2,826 mothers. Broken down into five-year periods, this was 1:1,489 for 1931 to 1935; 1:5,041 for 1936 to 1940; and 1:7,755 for 1941 to 1945.

TABLE VI

| | PRE-ECLAMPSIA | | ECLAMPSIA | | NEPHRITIS | | HYPERTENSIVE | |
|------------------------|---------------|---------------------|-----------|---------------------|-----------|---------------------|--------------|---------------------|
| Weight of baby | 1475 | 3277 Gm. 7.2 lb. | 51 | 2781 Gm. 6.1 lb. | 10 | 2860 Gm. 6.3 lb. | 273 | 3269 Gm. 7.2 lb. |
| Stillborn | 47 | 3.1% | 10 | 18.1% | 4 | 33.3% | 13 | 4.7% |
| Neonatal death | 23 | 1.5% | 4 | 7.2% | 1 | 8.3% | 4 | 1.4% |
| Twins r:ratio | 40 | 1:36.4r | 4 | 1:13r | — | — | 3 | 1:94r |
| Maternal deaths | 5 | 0.34% | 4 | 7.86% | 1 | 8.3% | 0 | 0.0 |
| Cardiac decompensation | — | — | — | — | — | — | 5 | 1.8% |
| Hydrothorax | — | — | — | — | — | — | 2 | |
| Acute pulmonary edema | — | — | — | — | — | — | 1 | |

Operative Deliveries.—These figures listed in Table VIII represent percentages of the infants delivered by operative means. The percentage incidence of operative delivery was shown in Figure 5 and was 23 per cent for the pre-eclamptic group; 56 per cent for the eclamptic; 33 per cent for the nephritic, and 11 per cent for the hypertensive. Prior to 1942, prophylactic forceps were not employed. Since that time, the general policy of the hospital has been the use of prophylactic forceps; and low or mid-forceps are used when the second stage has reached two hours in primiparas, or one hour in multiparas, or if an indication for immediate delivery arises. Only the low cervical type of cesarean section has been employed during the last three years. Version and extraction

a medical emergency that demands immediate and adequate therapy to prevent loss of life. With adequate rest, which may mean absolute bed rest for the last two or three months of gestation, these patients can usually be safely carried to term.

Summary and Conclusions

1. Eighteen hundred cases of elevated blood pressure during pregnancy have been presented.

2. The teaching of the importance of adequate pre-natal care in order to detect symptoms of impending toxemia at their first appearance cannot be over-emphasized.

3. Prevention of eclampsia is of paramount importance, since the maternal and fetal mortality rises in direct proportion.

4. Nephritis and pregnancy are poor cohorts, as the maternal risk is high and the fetal salvage is low.

5. The incidence of twins in pre-eclamptic and eclamptic toxemias is found to be increased.

Reference

1. Davis, M. E., and Gready, T. G.: AM. J. OBST. & GYNEC. 51: 492, 1946.

Discussion

DR. W. J. DIECKMANN.—Findings reported are essentially the same as most investigators have found. The essayists used only an elevated blood pressure as their differential point. I wish to know why they did not use edema and albuminuria in addition.

I do not think diagnoses should be based on just the hospital stay. They should be deferred for at least four months, better six months, or even longer. The ideal is after another pregnancy.

Does the fetal mortality include all pregnancies or only those who went to term? We find that many toxemic patients abort in early pregnancy.

Our incidence of toxemia has not decreased during the last ten years. However, we do have eclampsia almost eliminated, having at the most one case per year. We have very few severe pre-eclampsies. The only ones that we now see are either the patient that has not been under care or has not been into the clinic for a number of weeks.

Since 1933 I have used the concept that patients who develop hypertension early in pregnancy or who develop it late in pregnancy without any abnormal weight gain and little or no edema or in whom the systolic blood pressure is over 200 have an essential hypertension. We have recently completed a follow-up of 600 patients who had two or more pregnancies in our hospital, the first of which was complicated by toxemia. Thirty-seven per cent had a recurrence of toxemia in the next pregnancy, and in these same patients three years later 51 per cent had a recurrence. As more time elapsed the incidence of recurrent toxemia and of hypertension increased progressively.

In some 1,700 toxemic patients we found that 42 per cent had pre-eclampsia or eclampsia, 53 per cent had hypertensive disease, 3 per cent glomerulonephritis, and 3 per cent nephrosclerosis in hypertensive patients. The authors had only 1 per cent hypertensive disease, which I think is far too low.

Dr. Dillon mentioned that it is not so much the amount of weight gained as it is the excessive amounts that the patient is gaining while under observation.

As the doctors in the clinic become more experienced watching for excessive weight gain, for increases in systolic blood pressure, our results in the treatment of these toxemic patients improve. The patients are put under dietary control and bed rest at an earlier date. They are hospitalized when they either do not cooperate or when their condition does

improvement in maternal mortality has been the result of various factors, viz., registration of the patients in the early months of their pregnancy; close observation by the attending staff during the patient's pregnancy, labor, and puerperium; institution of treatment when symptoms of toxemia first appear; and individualization of each case, with constant re-evaluation of her physical status while she is under the hospital's management. Table X shows a comparison of the cases at the Chicago Lying-in Hospital and the Lewis Memorial Maternity Hospital. These figures were obtained from a paper read before this society by Davis and Gready¹ in February, 1945, and cover a period from 1931 to 1944. The incidence of convulsive toxemia was 0.18 per cent in both institutions. However, our maternal mortality rate at Lewis was 3.3 per cent higher. The maternal mortality rate from all causes is almost identical in each institution.

TABLE X

| | CHICAGO LYING-IN | LEWIS MEMORIAL MATERNITY |
|-----------------------|------------------|--------------------------|
| PERIOD | 1931-1944 | 1931-1945 INCL. |
| TOTAL CASES | 47,945 | 28,263 |
| Eclampsia | | |
| Cases | 86 | 51 |
| Per cent | 0.18 | 0.18 |
| Deaths | 4 | 4 |
| Mortality, per cent | 4.6 | 7.9 |
| Total maternal deaths | 81 | 50 |
| Mortality, per cent | 0.17 | 0.176 |
| Per 10,000 mothers | 17.0 | 17.6 |

The statistics presented are almost all self-explanatory, and further discussion will be limited to only a few subjects.

Although an attempt is made to control excessive weight gain in all patients, it is the patient that shows a sudden increase during the last trimester that causes the greatest concern. This sudden gain is usually due to water retention. The other three most common causes of excessive but gradual weight gain during pregnancy are (1) the person of large stature who had purposely kept herself underweight by eating an inadequate diet, (2) the individual who develops an endocrine obesity, and (3) those who eat too much.

The incidence of ankle edema was tabulated because it is the symptom that the patient first notices. Patients having hypostatic congestion of the venous vessels, and patients during extremely warm weather may have this complaint also.

Epigastric pain in the hypertensive group is probably on the basis of passive congestion of the liver and splanchnic circulation. When present, early cardiac decompensation should be suspected. When present in the pre-eclamptic patient, it usually means that convulsions are imminent.

However, all symptoms, physical findings, and laboratory findings serve merely as gauges registering the degree of the underlying toxemia. Treatment of the symptoms and not the underlying cause is comparable to breaking the thermometer on the dashboard when the engine is overheating.

The absence of maternal deaths in our series of hypertensive cases does not detract from the seriousness of this complication. Acute pulmonary edema is

ANTICOAGULATION THERAPY WITH HEPARIN/PITKIN MENSTRUUM IN THROMBO-EMBOLIC DISEASE COMPLICATING THE PUERPERIUM AND GYNECOLOGIC SURGERY*

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Jewish Hospital of Brooklyn)

DURING the past three years or more, 251 patients with venous thrombo-embolic disease received subcutaneous heparin in the Pitkin menstruum with gratifying results.¹⁻⁵ Fifty-three of these 251 subjects were obstetric or gynecologic patients. In view of this rather extensive experience, it seemed opportune to report our results with heparin/Pitkin menstruum in the treatment of thromboembolism complicating the puerperium and gynecologic surgery.

Clinical Material

Most of the 53 patients (Table I) in this study were referred to the Thrombo-embolic Disease Unit by the Gynecological and Obstetrical Department of the Jewish Hospital.†

TABLE I. HEPARIN/PITKIN MENSTRUUM IN THE TREATMENT OF 53 PATIENTS WITH THROMBO-EMBOLIC DISEASE COMPLICATING THE PUERPERIUM AND GYNECOLOGICAL SURGERY

| CLASSIFICATION | NUMBER OF PATIENTS | NUMBER OF PATIENTS WITH PULMONARY EMBOLIZATION | DEATHS DUE TO PULMONARY EMBOLIZATION |
|---|-----------------------|---|--|
| Prepartum thrombophlebitis | 1 | 0 | 0 |
| Postpartum thrombophlebitis | 29 | 7 | 0 |
| Postoperative thrombophlebitis and/or phlebothrombosis | | | |
| Cesarean section | 4 | 1 | 1 |
| Hysterectomy | 15 | 9 | 0 |
| Vaginal Plastic | 4 | 1 | 0 |
| Totals | 53 | 18 | 1 (1.8%) |

Thirty-four of these 53 patients were obstetric, and 19 presented gynecologic problems. One of the 34 parturients received the treatment for phlegmasia alba dolens which developed forty-eight hours prior to the onset of labor; the therapy was interrupted during the actual labor and restarted in the postpartum period. Of the remaining 33 parturients, 29 were delivered vaginally and 4 by cesarean section. Eight of the parturients embolized prior to therapy, in two instances despite femoral vein ligation. Two patients were dicoumarol failures prior to inaugurating subcutaneous heparin/Pitkin menstruum therapy.

Manifestations of thrombo-embolism were present in 19 postoperative gynecologic cases; 15 following abdominal hysterectomy and 4 following vaginal plastic procedures. Ten in this group had one or more pulmonary emboli prior to the heparin therapy; in four patients despite vein ligation.

*Presented in part at a meeting of the Brooklyn Gynecological Society, Oct. 11, 1946.

†We wish to thank the Department of Obstetrics and Gynecology for referring this clinical material.

not seem to improve with ambulatory treatment. They may be hospitalized several times in the pregnancy. Any time after 32 weeks, which we consider the period of viability, the pregnancy is terminated if the signs or symptoms warrant it. After 36 weeks we are guided by the severity of the toxemia and the condition of the cervix as determined by vaginal examination. If the cervix is soft and dilated, we rupture the membranes. If there is no dilatation, we may continue medical management in the hospital for a period of five to ten days, examining the patient periodically and, as soon as there is some dilatation, the membranes are ruptured. In most instances, cesarean section for toxemia is an admission that either the patient did not cooperate or that treatment in the clinic or in the hospital was not instituted early enough and intensively enough. We believe it is better to perform a cesarean section under local anesthesia in the pre-eclamptic patient who is having symptoms along with signs (severe toxemia) than to wait until that patient has eclampsia or fetal death or an abruptio placenta.

DR. DILLON Closing).—In answer to Dr. Dieckmann's question, blood pressure was not taken as the sole factor in deciding which were the pre-eclampsies. All of these records were reviewed, and many were reclassified. In some cases this was difficult because of registration at the clinic late in pregnancy, and failure to have adequate follow-up. Our follow-up has been much better in the past few years; and it has been left out with the idea of presenting that in a separate paper at a later date. In the opening portion of the paper, I mentioned that the pre-eclamptic group would include some hypertensives. Had the follow-up been adequate, or had the patients registered in the first trimester, I am certain the incidence of pre-eclampsia would be less, and of hypertension greater.

These figures did not include cases of early abortion. For some reason, we were not seeing these cases. They were evidently going elsewhere. There were some cases of late abortion.

The low incidence of demonstrable edema may have been a result of failure to record its presence on the prenatal record. It is only in the last three years of this study that *all* patients with a pressure over 140/90 are admitted to the hospital, and a complete history and physical done. Some of the eclampsies made their first appearance at the hospital at term, and in a convulsive state in the first years of the hospital's operation. There was one multipara, a gravida iii, para ii, who had convulsions in her first pregnancy, then a normal pregnancy, and then eclampsia in her third pregnancy.

5. Be certain that the contents of the syringe are not too hot prior to the injection. The syringe and contents should feel only slightly warm.

6. Do not apply either heat or cold to areas of deposition unless for purposes of accelerating or retarding release of the drug.

Clinical Use.—In the average case use the entire contents of one 3 c.c. ampule containing 300 mg. of heparin sodium salt. This dose should be sufficient to keep the patient "heparinized" for approximately two days (Fig. 1). Therefore, administer the contents of one 3 c.c. ampule every second day throughout the requisite period of heparinization. If the patient receives a blood transfusion during the period of heparinization, administer the contents of one 3 c.c. ampule immediately following the transfusion, irrespective of when or how many previous deposits have been given. If, for any reason, there is need to stop the effect of heparinization, this can be accomplished immediately by the intravenous administration of 250 to 500 c.c. of whole blood or bank blood not more than three days old.

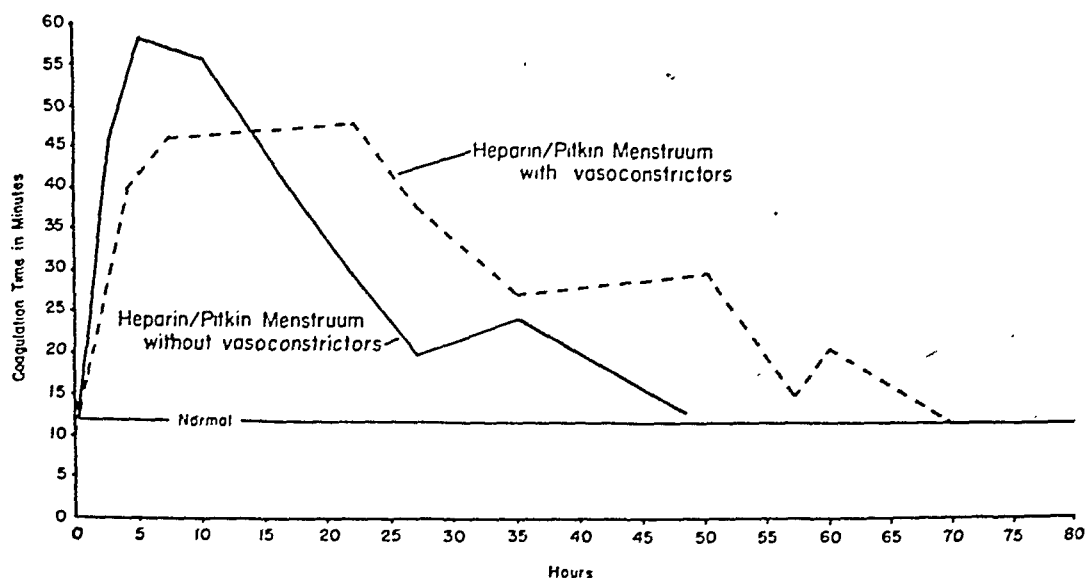


Fig. 1.—Coagulograms; demonstrating average prolongation of coagulation time following the administration of 300 mg. of heparin/Pitkin menstruum.

Method of Following the Patient's Clinical Course.—The effect of heparin is judged by and based on determination of the blood coagulation time which should be estimated daily throughout the period of heparinization. The capillary tube method is inaccurate and should not be used. The Lee-White modification of Howell's method for determination of blood coagulation time is recommended. The technique of performing and estimating coagulation time is as follows:

1. Place four chemically clean, dry 75 by 10 mm. test tubes in a rack.
2. With a sterile, dry syringe and needle, withdraw about 2 c.c. of venous blood from the subject. The test is timed from the moment the blood is first observed in the syringe. Remove the needle from the syringe.
3. Gently distribute approximately 0.5 c.c. of blood into each test tube. Discard the last air-containing fraction.
4. All glassware, syringes, and needles must be absolutely dry. Moisture, alcohol, etc., invalidate the determination.
5. The vein must be negotiated cleanly. If difficulty is encountered, it is best to use a fresh needle and syringe. Even a small amount of tissue juice aspirated into the syringe will give a false result.

Treatment Program

The treatment program which follows was that adopted for venous thrombo-embolism as previously reported.²⁻⁵

Formulae for Clinical Use.—The ampules* for clinical use (Table II) are as follows:

Heparin/Pitkin Menstruum (V. C.)

ampules, 2. c.c.—each ampule containing 200 mg. heparin sodium salt with vaso-constrictors.

ampules, 3 c.c.—each ampule containing 300 mg. heparin sodium salt with vaso-constrictors.

Heparin/Pitkin Menstruum (Plain)

ampules, 2 c.c.—each ampule containing 200 mg. heparin sodium salt; no vaso-constrictors.

ampules, 3 c.c.—each ampule containing 300 mg. heparin sodium salt; no vaso-constrictors.

Dosage Plan.—In general, body weight and individual reactivity dictate the amount of heparin/pitkin menstruum to be used in a given case. For the initial injection, body weight may be used as a guide. Patients weighing up to approximately 150 pounds (67.8 Kg.) should be given an initial dose of 300 mg. of heparin sodium salt, patients over this weight should be given an initial dose of 400 mg. Subsequently, the dosage should be adjusted according to the intensity of the "heparin effect" as estimated by the coagulation time. Compared with a normal coagulation time of nine to fifteen minutes (Lee-White modification of Howell's method), a coagulation time of thirty to sixty minutes is considered an adequate "heparin effect." In actual practice it will be found that a conventional dose of 300 mg. of heparin will suffice for about 90 per cent of subjects who are normal reactors. The remaining 10 per cent are either hypo- or hyper-reactors requiring 400 or 200 mg. dosages respectively.

Method of Administration.—1. Warm the ampule gently by either holding it under running hot tap water, or immersing in a container of hot tap water until the contents become fluid.

2. Shake thoroughly to disperse any precipitated material.

TABLE II. HEPARIN/PITKIN MENSTRUUM FORMULAS

| | WITH VASOCONSTRICTORS | | WITHOUT VASOCONSTRICTORS | |
|--------------------------------|-----------------------|-------|--------------------------|-------|
| Heparin, sodium salt, mg. | 300.0 | 200.0 | 300.0 | 200.0 |
| Epinephrine hydrochloride, mg. | 1.0 | 1.0 | 0 | 0 |
| Ephedrine sulfate, mg. | 25.0 | 25.0 | 0 | 0 |
| Chlorobutanol, mg. | 0.5 | 0.5 | 0.5 | 0.5 |
| Eucupin dihydrochloride, mg. | 1.0 | 1.0 | 1.0 | 1.0 |
| Pitkin menstruum, c.c. | 3.0 | 2.0 | 3.0 | 2.0 |

3. Draw the contents of the ampule into a dry, sterile 5 c.c. or 10 c.c. syringe, using a sterile needle, gauge 18 (2-inch length). After the contents have been drawn up, the 18-gauge needle should be replaced by a 20-gauge needle for the actual injection.

4. Inject the contents immediately into the deep subcutaneous (or superficial intramuscular) tissue, preferably in the anterior or lateral aspect of the thigh. When subsequent injections are required, use the right and left thighs alternately and avoid sites of previous injection. Do not inject into sites where pressure may be exerted upon the injection area.

*Prepared and distributed by William R. Warner & Co., Inc., New York.

3. Digitalis is said to inhibit the anticoagulant action of heparin. If possible, avoid the use of this drug during period of heparinization.

4. If suspension of heparin activity is desired, small transfusions of whole blood or relatively fresh bank blood will inactivate any circulating heparin. An ice bag to the site of deposit, or a tourniquet above it will suspend or slow up the absorption of the drug. In our experience the use of protamine for abrupt interruption of heparinization has not been necessary.

5. In hypertensive patients or those with myocardial disease, it is preferable, although not mandatory, to use heparin without vasoconstrictor drugs in order to avoid the transitory subjective vasoconstrictor effects.

Suggestions for Treatment.—1. In cases of thrombophlebitis, it is advisable to inject the heparin into the thigh which is normal. Avoid using the affected thigh for deposition of heparin until the swelling has partially receded.

2. For hyperreactors employ the 2 c.c. ampule which contains 200 mg. of heparin sodium salt. For hyporeactors administer 400 mg. This is accomplished by combining two 2 c.c. ampules each containing 200 mg. of heparin sodium salt. Where vasoconstrictors are indicated use only one ampule with vasoconstrictors in the combination inasmuch as the amount of vasoconstrictor drugs contained in the one ampule will suffice for the entire dose of heparin.

3. As a general rule for effective heparinization the blood coagulation time should be not less than two to three times the control coagulation time, i.e., thirty to forty-five minutes as contrasted with a control time of nine to fifteen minutes.

Adjuvant Therapy.—Coincident with the institution of heparin therapy the liberal use of papaverine is recommended, 1 to 3 grains every four hours intramuscularly or even intravenously and, later, maintenance dosages by mouth. Smoking is strictly prohibited. Paravertebral block, although used extensively in arterial occlusions, is not used by us in thrombophlebitis as a routine measure since we have found that venous spasm disappears promptly following administration of subcutaneous heparin.

While the addition of antibiotics and/or sulfonamides to the treatment program is not discouraged, these are not necessary in the management of the usual type of thrombo-embolism encountered in obstetric and gynecologic practice. Should, however, there be any identifiable infective etiology, the antibiotic and/or chemotherapeutic program should then be pursued intensively consistent with the nature of the infective organism. The mere presence of a febrile reaction does not connote bacterial invasion and may well be attributable to the mere presence of intravascular thrombosis particularly when the blood clot engages the vessel wall and precipitates an inflammatory intimal reaction.

Results

The clinical deportment of heparin/Pitkin menstruum has been observed in 53 patients (Table I) representing all forms of venous thrombo-embolic disease encountered in obstetrical and gynecologic practice.

The span of treatment for uncomplicated thrombophlebitis and/or phlebotrombosis was ten days to two weeks. For patients with pulmonary embolization, an additional week or two of therapy was required depending upon the extent of pulmonary infarction. In any event, the full heparin effect was present when the patient was first allowed out of bed.

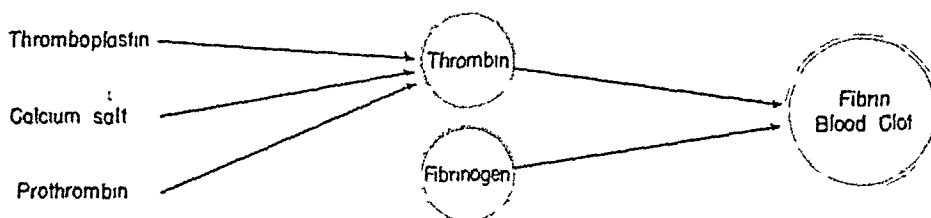
The results in this series were satisfactory as judged by effective control of pulmonary embolization, marked amelioration of pain and discomfort, rapid recession of edema, reduction in morbidity, acceleration in convalescence, and virtual absence of residual edema, particularly when patients were treated without delay.

6. Once the blood is placed in the test tubes, they must be disturbed as little as possible while observing for the end point. It will be noticed that well-heparinized blood will sediment very rapidly. The tubes should not be shaken after sedimentation of the blood. Look for clotting in the red cell layer as well as in the plasma layer, by gently tilting the tubes. In unclotted blood the red cell layer will flow as the tube is angled.

7. First, gently tilt one tube and note the flow of the red cell layer. If the flow is rapid, discard the tube and wait about five minutes before the second tube is angled. In this way the end point may be approximated, and then finally accurately determined from the third or fourth tube. Once any of the tubes are disturbed, they should be discarded.

8. The patient's coagulation time should be determined before heparinization for control purposes. After that the coagulation time should be estimated daily (twenty-four hours after the heparin injection and immediately before the next heparin injection).

NORMAL COAGULATION



MULTIPLE ACTION OF HEPARIN

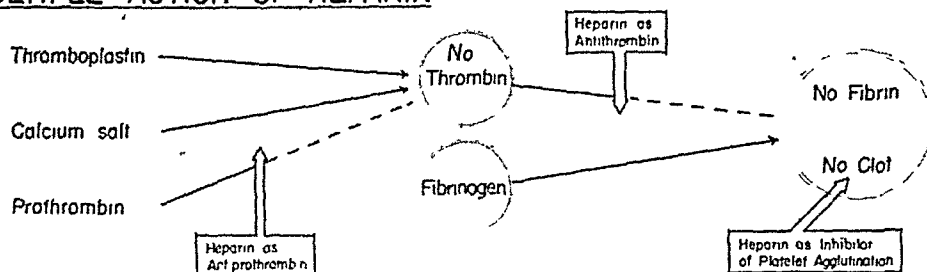


Fig. 2.—Mechanism of anticoagulant action of heparin.

Reactions, Complications in the Use of Heparin/Pitkin Menstruum.—1. The local pain, swelling, and tenderness of the earlier preparations is ascribable to the precipitate which was found to be a combination of heparin and eucupin. The pain factor induced by this precipitate was at times excessive but could be controlled by careful buffering so that the pH of the gel is more physiologically acceptable, and the tendency to precipitation noted in the original ampules is overcome. Other side-effects of the heparin/Pitkin menstruum preparations are trivial.⁶ On rare occasions some oozing will occur from the needle puncture. In the several thousand deposits that have been made in over 400 patients with various thrombotic disorders, there was but one instance of hematoma of sufficient proportion to justify interruption of heparinization in a patient with postpartum thrombophlebitis. The patient made an uneventful recovery.

2. Following the administration of a dose of 200 mg. or 300 mg. of heparin sodium salt combined with vasoconstrictor drugs, the patient will occasionally complain of palpitation and nervousness. These reactions require no treatment and disappear within a short time.

we have expended a great deal of time and effort in an endeavor to detect the potential clotter, the thrombophiliae. A straw in the wind is the report by Morrison, Richter, and Loewe on blood platelet clustering.¹¹ The report deals with the method and interpretation of a proposed clustering test. Clustering and/or increase in numbers of platelets is directly proportional to their coagulability. The most obvious characteristic of the blood platelet is its clustering propensity.^{12, 13} A simple routine blood platelet clustering test was devised as a means of establishing the coagulative status of individuals in comparative health and in disease. In a study of 200 subjects, a correlation between this test and thrombo-embolism was indicated. Its value as a means of detecting the clusterer, the thrombophiliae, and potential clotter, was suggested. The presumptive thrombophiliae and potential clotter identified by blood smear may then conceivably be protected by proper anticoagulation measures during pregnancy and infections prior to anesthesia and pre- and postoperatively. Clinical and experimental investigations of the role of blood platelet clustering in health and disease is being pursued.

While the use of anticoagulants preoperatively is not generally advocated at present, its prepartum use has been suggested in recent reports.^{14, 15} Our own related experience with heparin/Pitkin menstruum in the obstetric wards may well suggest its ultimate adoption as a prophylactic prepartum measure. A brief review of this experience has already been presented.

The routine use of anticoagulation therapy as a prophylactic measure must await further clinical and experimental investigation. Many methods of treatment of thrombophlebitis and/or phlebothrombosis have been proposed, although two major thoughts have dominated the clinical scene during the past five years; namely, vein ligation and anticoagulation therapy.

In the past, medical therapy in the form of sedation, rest, elevation, and mobilization of the offending limb has only caused long and permanent disability and, to say the least, anxiety to the clinician. The latter could only hope and meditate that his patient would not embolize. When the latter did occur a fatal outcome was often inevitable.

The Ochsner-DeBakey treatment¹⁶ of thrombo-embolism with paravertebral block reduces the pain by relief of vasospasm. Repeated blocks are necessary but the over-all length of disability and permanent disfigurement are not necessarily lessened. Papper and Imber¹⁷ have recently presented evidence that the use of paravertebral block may be so effective in producing vasodilatation that thrombi may be liberated with resultant embolism.

While our contrary views on the matter of vein ligation have been set forth elsewhere³⁻⁵ the literature abounds in articles advocating this form of therapy for venous thrombo-embolism.

The surgical approach to the problem of venous thrombo-embolism centers around ligation of the deep femoral veins, iliac veins, ovarian veins, or the inferior vena cava. Bilateral femoral vein ligation must be practiced, inasmuch as with unilateral vein ligation, fatal pulmonary emboli may derive from an unsuspected thrombotic process on the contralateral side. Even this procedure,

Most informative are the statistics with respect to the patients who had pulmonary embolization. There were 18 patients in this group with but one fatality, representing 1.8 per cent of the entire series of 53 patients and 5.5 per cent of the 18 patients who had suffered from one or more episodes of pulmonary embolization.

The treatment failure followed sequential femoral vein ligation for recurrent pulmonary embolization incidental to phlebothrombosis following operation for premature separation of the placenta. Subcutaneous heparin was discontinued prematurely two days after the initial left femoral ligation because the pulmonary findings were attributed to virus pneumonia, which was prevalent at the time. The right femoral vein was ligated about ten days after the left femoral vein ligation. Lethal massive pulmonary embolization ensued on the third day following the right femoral vein ligation. Necropsy disclosed old adherent thrombi in the left iliac and left hypogastric veins which were probably the source of the emboli found occluding the right pulmonary artery and main branch of the left lower lobe.

This fatality, the only one in this group of gynecologic and obstetric patients, must be catalogued as a treatment failure for both vein ligation with thrombectomy and supplemental subcutaneous heparin therapy, although the latter was suspended after much too short a span of treatment.

One of the obstetric patients suffered a hematoma at the site of one of the injections which did not interfere with the progress of the treatment program, the patient making an uneventful recovery. In this patient, as in all the other patients treated in the early stages of the disease, the hospital stay was definitely curtailed and the disfigurement eliminated or significantly reduced.

Discussion

The incidence of thrombo-embolic disease varies considerably with individual clinics. A representative statistical review of 6,114 gynecologic operations done at the Breslau Woman's Clinic disclosed 134 (0.19 per cent) cases of thrombo-embolic disease.⁷ There were 26 fatal embolic cases in this group, with an incidence of 0.42 per cent. A similar study of 10,297 obstetric cases, including 973 premature labors and abortions, revealed 102 (0.98 per cent) thromboembolic cases. In this group there were six fatal emboli, an incidence of 0.05 per cent. The Maternal Welfare Committee of Kings County recorded 395,655 deliveries from 1938 through 1945.* There were 794 maternal deaths in this group, of which 89 (8.9 per cent) were embolic. This represents one maternal death in 4,400 deliveries, and an average of 11 embolic deaths for each year of the report.

A detailed discussion of the functional pathology and etiology of venous thrombo-embolism is beyond the scope of this report. A comprehensive review of experimental studies and clinical observations in connection with this problem has been presented in previous publications.^{1-5, 8} Where a cause may operate to produce thrombophlebitis and/or phlebothrombosis, it should be elicited and removed whenever possible.

Despite early ambulation in the postoperative and postpartum patient, there is an irreducible occurrence of venous thrombo-embolism.^{9, 10} The widespread routine use of anticoagulation therapy in the prospective surgical and obstetric patient, while ideal, is not practical or feasible at present. As a result

*Personal communication.

fresh blood alone do not arrest the hemorrhagic tendency occasioned by the drug. Massive dosages of vitamin K are required which may, in turn, reinduce thrombosis.²⁴

In summary then, the delayed action, potential hazards, the unpredictable treatment failures, and the requisite complicated but indispensable laboratory procedures militate against dicoumarol as the anticoagulant of choice.

The properties of heparin which render it uniquely applicable in thrombo-embolic disease may briefly be enumerated; it prevents, with the aid of a plasma co-factor, the conversion of prothrombin to thrombin; it forms with serum albumin a strong antithrombin; and, finally, it prevents the formation of thromboplastin from platelets.²⁵ The accepted knowledge concerning the mechanism of the action of heparin is graphically portrayed in Fig. 2.

According to Jorpes²⁶ heparin is a mucoitine polysulfuric acid. The most potent preparations of heparin contain 45 per cent of sulfuric acid which results in an exceedingly strong negative electric charge. No other compound of high molecular weight in the mammalian body has such a strong electric charge. Apparently, heparin exerts its action through this charge. This seems to be supported by the neutralizing effect of basic protamine, which has the property of promptly counteracting the action of heparin. The multiple effect of heparin on thromboplastin, prothrombin, thrombin, the hemolytic complement, iso-hemagglutinins, and different enzymes is most readily explained as a loading and unloading of electric charges on the proteins concerned. The properties of heparin predicate the fact that a clot, regardless of its site or stage, cannot propagate in the presence of heparin. However, what happens to the clot which is already present?

It has been possible to determine experimentally in animals at what stage of clot formation heparin administration results in solution of the clot and what effect heparin has on the organized clot.^{4, 8}

Briefly, studies on the effect of heparin in experimental venous thrombosis in the rabbit have yielded the following data:

1. Red cell clots not organized and containing a minute amount of fibrin (sludge stage) disappear completely under heparin therapy.
2. Heparin therapy maintains patent adjacent collaterals and tributaries which ordinarily would become involved in the thrombotic occlusive process. These compensatory collaterals often become as large as the originally occluded vessel. This phenomenon has not been observed in control animals. It may be assumed, though not necessarily proved, that these processes also occur in obstructed lymphatics.

Until recently the routine use of heparin has been limited by the expense, by the huge amount of drug required in the individual case, and by the cumbersome method of administration which requires a continuous venoclysis or repeated daily intravenous dosage. The restriction of motion of the patient, the almost absolute certainty that superficial angitis would eventually occur at the site of injection, and the haphazard control of the clotting time rendered heparin therapy useless unless constant untiring supervision were available.

the magnitude of which is unduly minimized by present observers, does not offer absolute protection against embolization. Allen, Linton, and Donaldson report six deaths due to emboli subsequent to femoral vein ligation in a series of 1,300 patients.⁹ There are, furthermore, known fatalities in which the offending embolus originated from the profunda femoris vein proximal to the site of ligation of the superficial femoral vein. Ligation of the inferior vena cava upon a critically ill patient carries a high mortality.¹⁸ Nurnberg¹⁹ collected 526 cases of inferior vena cava ligation for puerperal sepsis with a mortality of 50.7 per cent. Since the favorite site for thrombophlebitis in the parturient and the postoperative gynecologic patient is situated in the venous plexuses about the uterus, adnexa, and pelvic veins, ligation below the femoral veins does not obliterate the focus. Finally, operative procedures which interrupt not only venous but also lymphatic channels contribute considerably to the production of edema. Ligation of the iliaes and inferior vena cava is frequently attended by late complications, permanent lymphedema of the lower extremities and neurovascular changes.

In view of the complications of the surgical approach in the treatment of thrombo-embolic disease, it is apparent that the anticoagulants assume prime importance. Anticoagulation therapy deals with the abnormal physiology of blood and lymph in the body. Of the anticoagulants dicoumarol and heparin have been the most widely used.

Recourse to dicoumarol is understandable because it can be administered orally. The effectiveness of the drug, however, is tempered by the difficulty in planning dosage schedules and, more important, because of its dangerous complications.²⁰⁻²⁴ There is great variability in the response to dicoumarol, this lack of uniformity of response being present even in the same individual. Fixed dosage schedules cannot be established; patients must be individualized. The action of dicoumarol is slow, from forty-eight to seventy-two hours being required before its therapeutic effectiveness is achieved. This delay in action is due to the fact that dicoumarol's anticoagulation action is a reflection of its attack on the liver inhibiting the formation of prothrombin.

Due to delay in action and the variability of the patient's response, dicoumarol is not always useful in the early critical stages of thrombosis or major pulmonary embolism where prompt anticoagulation effect is imperative. The delayed action and prolongation in effect after cessation of therapy are disadvantages during or shortly after operative procedures and in patients with anticipated, threatened, or actual hemorrhage. Instances have been observed in which embolism, thromboses, or progression of existing venous thromboses have occurred despite low blood prothrombins induced by dicoumarol.²² Patients receiving dicoumarol require daily prothrombin determinations. The use of dicoumarol should not be countenanced unless there are proper laboratory facilities for prothrombin determinations by acceptable techniques. The latter are time consuming and relatively expensive.

In the presence of liver disease the use of dicoumarol is contraindicated. It has been attended by irreversible hemorrhage and death.²³ Transfusions of

flexion and, if pain is induced (Homans sign) it is very significant of deep venous thrombosis. Because of the difficulty of establishing the normal standard; we have abandoned the routine clinical use of phlebography.²³

It is evident from a critical review of our series of patients that a comprehensive trial of subcutaneous heparin in the Pitkin menstruum has been carried out with good results. While other expedients, such as sulfonamides and penicillin, may be used in conjunction with it, heparin alone in clinically established thrombophlebitis, irrespective of etiology, is attended with consistent, beneficial, if not dramatic results. These include diminution of temperature, pain, and swelling which often become manifest within a few hours after initiation of therapy. This improvement is predicated on the limitation in the progress of the formed thrombus, while the original inflammation expends itself, and the thrombus either resolves or becomes organized. Since there is no further actual propagation of thrombus, there is a rapid and marked diminution in vasospasm. In all cases, morbidity is lessened and convalescence accelerated. It is felt that prolonged, deforming, and incapacitating edemas are further prevented in these patients by keeping lymphatics patent.

As has been described earlier, the general systemic anticoagulation effect of heparin seems to us to be a more rational therapeutic weapon than local vein ligation, especially when the precipitating cause of thrombosis is not yet known and the initiating site of thrombosis can be ascertained in many cases only by vague and indeterminate clinical signs.

Summary and Conclusions

1. Experimental investigation and clinical observation indicate that heparin plays a vital role in arresting the progress of intravascular thrombosis and promotes restoration of the vascular stream. It also enhances collateralization.

2. Two hundred fifty-one patients with various forms of venous thrombo-embolic disease have been treated with heparin/pitkin menstruum. This series included 53 subjects who were obstetric or gynecologic patients. Thirty-four of these 53 patients were obstetric, and 19 presented gynecologic problems.

3. The treatment of venous thrombo-embolic disease with subcutaneous heparin in the Pitkin menstruum was attended with lessened morbidity, prompt and rapid clinical improvement, and little or no residual edema. The causative factors responsible for the one treatment failure have been analyzed. Treatment failures with other methods have subsequently ended in recovery following the routine administration of the heparin/Pitkin menstruum preparation.

4. As a result of observations of its clinical deportment, the subcutaneous administration of heparin in the Pitkin menstruum is recommended as a safe, simple, practical, and effective method for anticoagulation therapy in thrombo-embolic disease complicating the puerperium and gynecologic surgery.

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In an attempt to achieve prolonged absorption of heparin, pellet and capsule implantation in experimental animals was attempted. Erratic, unpredictable effects were observed. However, a slower and more equable distribution of heparin was obtained by incorporation of the drug in the Pitkin menstruum developed to regulate the rate of release of water soluble drugs injected intramuscularly or subcutaneously.^{1, 2}

The ingredients of the pitkin menstruum are gelatin—15 to 30 per cent, dextrose—5 to 12 per cent, glacial acetic acid—0.5 per cent, and sufficient distilled water to make 100 per cent. The rate of liberation of the contained heparin is inversely proportional to the viscosity of the menstruum; the optimum percentage of gelatin and dextrose were found to be 18 and 8 per cent, respectively, for the preparation containing heparin. The technique for the use of the heparin/Pitkin menstruum preparation has already been considered.

For optimum results heparin therapy should be inaugurated as early as possible. The advantages of preventing spread of thrombosis before it can give rise to pulmonary embolism or serious local damage are obvious, and has been stressed repeatedly in the literature.²⁷ Admittedly, thrombo-embolism may be a treacherous and unpredictable condition; at times it occurs catastrophically and without warning. Nevertheless, if one is alert for slight premonitory signs, these will be discovered more often than has been supposed. One such diagnostic sign, described by Allen,²⁸ is an inexplicable rise in the pulse, temperature, and respiration at the same reading or observation. Where, after operation, these have shown the normal downward course, any fresh rise, however small, after the fourth or fifth day, must always evoke suspicion. Another sign sometimes observed is an unaccountable feeling of disquietude and restlessness which affects the patient. Or she may state, perhaps not until questioned, that she was kept awake during the night by a faint ache and a feeling of cramp in one of the calves, so-called "charley horse," a symptom which may already have disappeared. Complaint of even a slight stitch or pain in the chest must arouse strong suspicion of pulmonary infarction which is confirmed if the patient develops an irritative cough or expectorates blood-streaked sputum.

If any of these general signs are noted, a detailed physical examination must be made to elicit the cause. Examination consists of palpation of the groins, inner aspect of the thighs, popliteal spaces, the calves, and the veins of the feet, looking for swelling and tender areas. Conspicuous signs need not necessarily be present. In early cases one may note only slight swelling of the lower leg, an increased glossiness and tension of the skin, a faintly cyanotic discoloration in comparison with the other leg, and prominence of the superficial veins of one leg as compared with the other. All these signs need not necessarily be present but, if one or more of them is observed, the probability of an incipient thrombosis is considerably increased.

The most important sign is direct tenderness in the calf, discovered by pressure with the palpating fingers. Such tenderness will be more significant if none is elicited when the muscles at the same level are compressed from side to side. An increase in the consistency of the muscular part of the calf is another customary feature of thrombosis. Finally, the foot is brought into dorsal

CANCER; EVOLUTIONARY REVERSION IN CELL METABOLISM

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IT IS proposed that cancer is essentially a reversion in cell evolution resulting from an abortive attempt of the regenerating cell to adapt itself to an environment that is deficient in one or more of the elements essential for the formation of the enzyme pattern it requires to become a fully differentiated specialized cell. *Recent studies have revealed a marked similarity in the enzyme patterns of embryonic and malignant cells.* There is also evidence to suggest that certain chronic low grade tissue vitamin deficiencies which result in impaired function of the normal adult cell, shift the metabolic balance in favor of the growth and development of a cell with an embryonic cell enzyme pattern. Growing cells must synthesize their vitamin containing enzymes from available constituents in their immediate environment. When the cell environment is marginally deficient, the relatively low concentration of one or more of these essential elements may not permit the synthesis of the usual adult cell enzyme systems, and yet may be entirely adequate for the synthesis of the enzyme pattern of an embryonic cell. When, in the face of such deficiency conditions, local tissue growth is continually forced in the repair response to a chronic irritant, the regenerating cells, if they are to survive, are forced to revert to the use of their embryonic cell enzyme pattern. It is suggested that when these factors, (a) chronic nutritional deficiency, marginal in character, and (b) continuously forced local tissue growth, obtain over a long period, the newly formed regenerating cells will by gradual stages revert morphologically as well as enzymatically and finally, after many cell divisions (cell generations), assume all of the behavior characteristics of the primitive embryonic cell.

Speculation on the possibility that malignant tumors are analagous to embryonic tissue goes far back to the earliest theories of cancer. It is only recently that experimental data supporting this idea have been forthcoming.

It has been shown by Burk,¹ and again by Greenstein and Thompson² in comparative studies on fetal rat liver, adult liver, and hepatoma that, metabolically; the malignant tissue closely resembles the embryonic in the extent of glycolysis, the activity of a number of different enzyme systems and in sulfur distribution. In these respects the fetal and *malignant* tissue are similar and differ significantly from the adult tissue. West and Woglom³ have shown the same paralellism between the biotin content of embryonic and malignant tissues. In some embryonic tissues the biotin content is higher than in the adult tissue, in others lower. They found "In all cases the biotin content of both tumor and embryo tissues deviated in the same direction from the corresponding normal." There was no evidence from their experimental work, however, that tumor growth was in any way dependent on biotin. Considering the similarity in their enzyme patterns, embryonic and malignant tissues must

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cell environment we regard as the *possible* initiating factor in the malignant process in many cancer producing tissues.

Evidence suggesting that marginal deficiency conditions and chronic inflammation are almost invariably associated with the development of one type of cancer in human subjects has been presented by one of us (J. E. A.).⁶ In a survey of 100 gynecologic patients, 50 with early uterine cervical cancer and 50 controls, chronic dietary deficiency was present in 90 per cent of the cancer patients according to both the dietary-history standard and the measure of thiamine excretion. Almost all showed evidence of chronic cervicitis. Evidence of similar nutritional status was found in only 10 per cent of the controls. This same dietary inadequacy, chronic in character and marginal in degree, associated with chronic inflammation, was also found in a high percentage of another group recently reported⁷ who had not yet developed malignant disease but exhibited evidence of morphologic changes typical of "pre-cancer" in the cells scraped from the squamocolumnar junction of the cervix.

The role of vitamins in enzymology and their relation to malignant disease has been the subject of many recent studies. Those which have been shown to be actual components of the enzyme equipment of the fully differentiated cell appear to be vitally related to the process of carcinogenesis. Certain members of the B group of vitamins, particularly riboflavin, niacin, and thiamine, are especially implicated.

The studies of Kensler and co-workers,⁸ elucidating the prominent role played by riboflavin in the protection of rats against hepatoma formation while on a diet containing p-dimethylaminoazobenzene, are outstanding in this field. Pollack and Taylor and associates⁹ have made an invaluable contribution to cancer research by compiling data on the vitamin content of normal adult and malignant tissues. They have shown that malignant tissues resemble one another in their content of various B-factors; and differ from the corresponding normal adult tissues in that their enzyme systems appear to require lower concentrations of riboflavin,⁹ thiamine,¹⁰ and niacin.¹¹ The similarities between embryonic and malignant tissues have been pointed out, and evidence indicating that the enzyme pattern of the embryonic cell, like the malignant cell, depends on relatively low concentrations of riboflavin and thiamine has been reviewed. Others have investigated vitamin metabolism and its relation to malignant disease in man. Martin and Koop¹² and Abels and associates¹³ have shown a close association to be present between intra-oral cancers, pre-cancerous oral leucoplakia, and B-complex deficiencies. Studies on uterine cancer showing the close association between this form of malignant disease and the existence of a chronic subclinical thiamine deficiency have been referred to above.^{6, 14}

The effects of a chronic hypovitaminosis on the cell tissue environment might be analyzed as follows: As a result of the deficiency the function of the fully differentiated cell is hampered because of an interference with certain of its enzyme systems. It is able to continue but a labored existence. On the other hand, all of the essential requirements of the embryonic cell, whose growth and efficient functioning apparently depend on lower concentrations of some of the B-vitamins, may be fully complied with. The sugges-

also coincide in their comparative content of certain other B vitamins. Burk¹ and Greenstein and Thompson,² in studies on liver tissue referred to above, have shown that many of the riboflavin containing enzymes are found in much lower concentrations in tumor and embryonic tissue than in the normal adult tissue. Robertson and Kahler,⁴ by assays on rat tissue, have presented actual data on the riboflavin content of fetal liver as compared to normal adult, normal regenerating liver, and hepatomas induced by various carcinogenic agents. With the riboflavin concentration of normal adult liver as standard at 100, regenerating liver also had a value of 100, fetal liver -19, and six hepatomas varied from 16 to 47. It is, therefore, evident that in the rat the tumor and embryonic tissue resemble one another in their content of riboflavin and contain considerably lower concentrations of this essential element than the corresponding normal adult tissue. Barnes,⁵ in studies of the cord blood, maternal blood, and placenta in human subjects, found that the concentration of thiamine in the cord blood is almost invariably lower than that in the maternal blood; and that placental tissue has a very low value for the concentration of thiamine. This suggests that the fetal embryonic enzyme pattern depends, again, upon a lower concentration of this B-factor.

In addition to the similarities in their enzyme patterns, many other resemblances between malignant and embryonic tissues have been noted. Morphologically, the similarities are striking; and their behavior characteristics are similar (both are rapidly growing tissues, and both can be heterologously transplanted). These resemblances strongly suggest that malignant tumors are formed from cells which have resumed certain embryonic characteristics in a disordered growth process.

One feature in these similarities which may be particularly significant is the fact that the enzyme systems of both embryonic and malignant tissues in comparison to those of adult tissues are apparently much less dependent on certain essential components of the B-complex which the regenerating cell must obtain from the constituents available in its immediate environment.

General body growth stops when any one essential component of new cells is not available. Focal growth activity, however, as a necessary part of the repair response to the stimulation of a chronic irritant, is forced under the pressure of the demand for new cells as important protective elements. According to the degree of the deficiency focal growth activity will be affected in different ways; when severe, no growth activity will take place regardless of the pressure of the demands of the repair process. However, if the deficiency is marginal, the chronic repair stimulus being continuous, the tissue may make an effort to form a supply of new protective cells from the limited materials available. In this action it must undergo an adaptation process and produce a cell which can survive in the "deficiency" environment. The results of studies on the enzyme systems of embryonic cells referred to above indicate that these cells can function adequately with lower concentration of certain B vitamins than the corresponding normal adult cell. A marginal deficiency for the adult cell would not be a deficiency state for the embryonic cell. In the adaptation process, therefore, an embryonic type of cell must be produced. This evolutionary reversion which has been conditioned by the local tissue response to a stimulus to regeneration in a marginal deficiency

mammary gland and those of the female generative tract where activities run in a physiologic cycle involving recurrent episodes of massive desquamation followed by rapid regeneration of tissue.

II. Tissue Vitamin Deficiency

Kensler and associates⁸ have shown that in the production of liver cancer with p-dimethylaminoazobenzine, in addition to cell destruction and a resultant repair response, there is an interference with an enzyme system—the enzyme system in which Coenzyme I is concerned. Riboflavin is essential for the efficient performance of Coenzyme I. One surmises that as a result of the interference with this enzyme system the usual metabolism of the regenerating cell is impossible. It loses the ability to perform many of its highly specialized functions and is forced to depend for its survival on other of its enzyme systems. These are presumably adequate for reproduction and growth, but lacking the total enzyme pattern of the fully differentiated cell, the new cell also lacks its highly specialized functional capacity. It is a cell which is adequate for more primitive functions only, viz., reproduction and growth. Its enzyme pattern is now so fashioned that all of the materials which enter the cell are used for growth and reproduction. It is a malignant cell. Riboflavin in large doses plus casein, or an adequate diet, will enable Coenzyme I to function properly in the regenerating cell and will almost completely annul the carcinogenic effect of p-dimethylaminoazobenzine. This suggests that one of the important aspects of p-dimethylaminoazobenzine activity as a carcinogenic agent is its effect in creating a relative riboflavin deficiency in an area where active regeneration is taking place; that it creates a relative deficiency of a factor necessary to the regenerating cell for the formation of the full enzyme pattern required for the performance of the specialized tasks of a highly differentiated cell.

Russell¹⁵ has shown that a diet deficient in thiamine and riboflavin will significantly decrease the induction period of tumor formation when the cells of the central nervous system of the rat are subjected to the effects of methylcholanthrene. In summary he states, "It is suggested that the altered metabolism of the cells of the nervous system resulting from the deficiency of thiamine and riboflavin caused the cells to respond more readily to the carcinogen."

There is, therefore, ample evidence that various vitamin factors are directly concerned with the propensity of the cell to become malignant. When deficient, the transformation is more readily effected. The fact that the functional activity of the new cell is not hampered in any way by the low vitamin concentration suggests that it is formed in the adaptation process. It is doubtful whether it is always one particular vitamin factor which is involved. It may at one time be one, at another time another. The essential feature is an interference with the enzymes necessary to the cell for the performance of its highly specialized functions. It has been shown that p-dimethylaminobenzine acts fundamentally in this manner. It is presumed possible, though not proved, that other agents which have been implicated in the production of malignancy may act essentially in the same fashion. The virus responsible for mammary

tion is that when these conditions are present at a focus of chronic irritation where cell division, in the process of repair and regeneration, is occurring repeatedly, eventually the regenerating cell will be forced to undergo a process of adaptation and will revert to the cell type which can function efficiently under the restricted conditions imposed. In the process of adaptation the cell, in effect, undergoes evolution in reverse and resumes after many cell divisions its embryonic characteristics. Once embryonic reversion has taken place, growth and invasion may occur under the influence of continued malnutrition or in response to various body growth hormones which have a selective stimulating effect on the tissue involved.

In studies on uterine cervical cancer,⁶ evidence has been presented suggesting that these three factors: nutritional deficiency, chronic infection, and hormonal stimulation, are important in the genesis of this malignant disease. Interpreting this evidence as applicable to carcinomatous disease in general and considering the many resemblances between malignant and embryonic tissues which have been demonstrated, three essentials in carcinogenesis might be described as follows:

1. The existence of a focus of chronic irritation where cell division as a part of the process of regeneration and repair is occurring repeatedly and as a body defense reaction must continue as best it can in spite of the nutritional environment.
2. A tissue vitamin deficiency that alters the cell environment making it impossible for the new cell formed in the process of regeneration to complete the enzyme equipment of the fully differentiated cell, but at the same time adequately fulfilling all of the metabolic requirements of an embryonic cell. These two factors operating over a long period cause the cell to undergo reversion and assume its embryonic characteristics.
3. A hormonal factor which acts upon the cell which has assumed its embryonic character enzymatically and morphologically and stimulates its further development, growth, and invasiveness.

I. Chronic Irritation

The importance of chronic irritation, mechanical or infectious, as a significant factor in the development of malignancy has long been recognized. As a focalizing factor it may have its effect in a number of ways. As a site at which continuous cell division is occurring it is the point at which cell changes conditioned by environmental factors will take place. As an area of hyperemia it will be an area that is subjected to increased amounts of any hormonal agent present in the blood stream. There is also suggestive evidence that inflamed cells or cells adjacent to an inflamed area are able to fix certain hormonal agents and thus cause a marked increase in their local concentration. This evidence has been reviewed and discussed in a previous publication.⁶

The concept suggested implies that some stimulus to cell division is absolutely necessary. This is in accord with the fact that malignant disease most commonly develops at sites of chronic irritation or in organs such as the female

do not act except upon the intact cell, we suggest that their action may be principally that of altering the permeability of the cell membrane to elements essential for the operation of the cell enzyme systems. A growth promoting hormone may permit essential elements required by the enzyme systems concerned with growth and reproduction to enter the cell. As more of the essential elements are made available, more activity and more growth is possible. While they are excluded the cell's enzyme systems, lacking energy material, remain inactive. Thus the neoplastic cell may remain dormant, its growth potentialities locked within because of the exclusion by the cell membrane of materials essential for growth. With a significant alteration in the body hormonal status a sudden alteration in the cell membrane takes place, materials essential for the operation of its enzyme systems are made available, and its growth potencies suddenly manifest themselves perhaps years after the formation of the neoplastic cell has taken place.

Significant changes in the body hormonal status may occur with age or with changes in the body nutritional status. In the hormonal changes of the climacteric there is often evidence of overactivity of some pituitary hormones as the depressant effect of the gonadal hormones on the pituitary is gradually withdrawn. There may be alterations in the pituitary growth hormone during this period. Nutrition has a marked effect on endocrine function.

Tannenbaum¹⁸ has shown that underfeeding causes a notable reduction in the incidence of mammary gland carcinoma in susceptible strains of mice. It has been pointed out that this effect is in large part, perhaps wholly, due to the secondary effects of caloric intake on endocrine gland activities. The production of estrogens is significantly reduced and the mammary gland is not subjected to the usually strong growth stimulating effect that this hormone exerts. There is evidence also that selective nutritional deficiencies may increase the amount of estrogen in the blood stream. Biskind and Biskind¹⁹ have shown that a B vitamin deficiency may result in impaired hepatic function with a resultant failure of the estrogen inactivation-excretion mechanism. In the patients with uterine malignancy referred to above,⁶ accompanying the thiamine deficiency evidence of high endogenous estrogens was consistently present in the character of the cervical cytology.

Inherited characteristics which determine the intensity of endocrine gland activity have an important bearing on the genetic aspects of carcinogenesis. It has been shown that the characteristics of endocrine gland activities as determined by hereditary factors is of significance in determining the susceptibility of certain strains of mice to the development of mammary gland carcinoma. There is, in addition, some unusual property of the nucleus-cytoplasm complex which we might say determines a ready tendency of the cell to undergo evolutionary reversion. This property is inherited and has not yet been explained. The possibility of genetic factors causing a peculiarity in general cell membrane permeability may also be worthy of consideration.

The Cell Enzyme Systems

In the production of hepatomas with p-dimethylaminoazobenzene, an interference with one set of enzymes results in the development of a cell that con-

carcinoma in mice may interfere with these enzymes. Neoplastic-producing x-rays may knock out this set of enzyme systems. It is known that porphyrins interfere with vitamin metabolism and that certain derangements in porphyrin metabolism are associated with some forms of malignancy.

The altered cell possesses the enzyme system of an embryonic cell—a system geared for growth and reproduction. We might then plausibly picture malignant disease as essentially a reversion to an embryonic type of cell metabolism conditioned by a change in cell environment. This change in cell environment results in the inability of the newly formed regenerating cell to complete the enzyme pattern it requires for the specialized functions of a highly differentiated cell. Its more primitive enzyme systems, however, which are adequate for division and growth remain intact. The cell, if it is to survive, is forced to revert enzymatically to the use of these embryonic enzyme systems. A cell that is stimulated in the process of repair and regeneration to repeated division in the deficiency environment will eventually revert morphologically as well as enzymatically to the embryonic state. Thus the malignant process is initiated, a neoplasm is formed. Under the influence of specific growth stimulating body hormones its growth characteristics will be determined. It may immediately assume the rapid growth properties and the invasiveness of a highly malignant growth if there is a potent enough growth stimulus present. On the other hand, the cells so changed may remain for years as a tiny neoplastic focus only to be activated some time later when the body hormonal balance is altered by some additional nutritional factor or by one of the hormonal alterations associated with stress or aging.

III. The Hormonal Agent

There has been considerable controversy as to the status of body hormones, e.g., estrogen, as carcinogenic agents. Being structurally related to the known carcinogens, benzpyrene and dibenzanthracene, the possibility that estrone and estradiol and related compounds possessed carcinogenic properties was readily inferred. Estrogens were shown to increase the frequency of the development of malignancy in the mammary gland and the female tissues of Müllerian duct origin of experimental animals when the other requirements for the development of these malignant growths were present. Estrogens alone, however, except in massive doses and over a prolonged period, would not produce malignant growths. And, as pointed out by Dodds,¹⁶ stilbestrol and hexestrol which do not possess the condensed carbon ring of estrone and the carcinogenic agents, but do possess the gynecogenic properties of estrogens, have the same influence in increasing the frequency of the development of these malignant growths. Therefore, the effect of estrogens in the production of these tumors is probably due purely to the marked growth effect which they exercise selectively on the tissues concerned.

Jensen and Tenenbaum,¹⁷ in a review on hormones and enzymatic reactions, conclude, "It appears that the action of hormones on the rate of enzymatic reactions takes place only in the intact cell. It is known that the activity of certain enzymes is dependent on cellular integrity." If hormones

velops in the cell as differentiation and specialization of function occur. They vary in concentration from tissue to tissue because of the functional variations from tissue to tissue. They depend upon relatively high concentrations of the B-vitamins for efficient performance. We may plausibly regard this group as a "prepotent" group which exercises a priority on the energy materials that are brought to the cell. Thus while they are intact energy materials are directed toward specialized functional activities and none are available for the secondary more "primitive" group. If the regeneration process results in the formation of cells that are unable to complete this set of enzymes because of cell environment deficiencies, all of the energy materials which are made available to these cells are used for growth and reproduction.

The existence of hypovitaminosis as an isolated fact, however, does not mean that the cell will eventually become malignant. It will probably remain morphologically the same although functionally impaired. However, if a cell which has retained the ability to reproduce itself—still possesses the primitive enzyme group—is confronted with a tissue environment characterized by a hypovitaminosis and is stimulated to repeated cell division, the vitamin deficiency will eventually, over a long period of time, impose a restriction upon the enzyme pattern which the newly formed cell can acquire. This will limit its capacity as a specialized differentiated cell and eventually, we submit, it will by gradual change become dedifferentiated until it has reverted completely to the embryonic form.

Reversion Process—Dallo's Dictum

There is a generally accepted principle in biology regarding the irreversibility of evolution which is known as Dallo's Dictum. It states that, so far as animal structure is concerned, evolution is irreversible but, regarding adaptation to a new environment simulating conditions which obtained in the past in another environment, evolution is reversible. Applying this principle to the regenerating cell confronted with an environment in which there is a deficiency of the elements required for its function as a highly differentiated cell but a plentiful supply of all of the elements required for the function of the capacities it exercised as an embryonic cell in the past it would appear that all of the factors conditioning evolutionary reversion are in operation.

There are a number of facts which appear to indicate that the transformation from a normal to a neoplastic cell is not an abrupt process but rather a gradual transformation involving a series of graded intermediate states. Roskelly and associates²² in studies on the biochemical changes which take place in this transition, have found that alterations in the cell enzyme pattern begin to appear long before it can be said that the tissue is malignant. The pathologist in his study of biopsy material frequently recognizes morphologic changes which give the cell an appearance intermediate between that of the normal and the neoplastic cell. To these he applies the term "precancerous." In the study of the cervical cytology smears of a large series of gynecologic patients by one of us⁷ the "precancer cell-complex" was encountered so frequently as to be considered a significant cytologic entity. As mentioned

tains only a part of the enzyme system of the fully differentiated parent cell. This part the liver cell used for growth and reproduction during its embryonic period. The enzymes which the cell in the regenerating phase would ordinarily acquire as it proceeded to differentiation have been kept from it. Occasionally, in the malignant transformation, not all of the specialized systems are interfered with and the cell, e.g., those of some prostatic carcinomas, possesses enzyme properties intermediate between those of an adult and those of an embryonic cell, but in its behavior characteristics it is more closely analogous to the embryonic cell.

In the malignant transformation it is doubtful if the cell ever acquires new enzyme systems, for there is always a loss of functional capacity. It re-develops or re-emphasizes enzymatic potencies already present which are of benefit for immediate survival in the existing environmental conditions. The fact that when the enzyme pattern which enables the differentiated cell to perform its specialized functions is destroyed or lost, the cell takes on the behavior characteristics that the remaining enzyme systems are best fitted to perform is not surprising. This suggests that one of the important mechanisms of internal cell control, keeping growth potencies within the cell in check, is the presence of the "specialized" enzyme systems. It is as if these systems exercised a priority demand on energy material within the cell and "starved" the particular enzyme systems that undertake the activities resulting in growth and reproduction. Once the specialized enzyme systems are interfered with, any food material entering the cell, the amount and character of which may be determined by the action of a hormone on cell membrane permeability, is immediately available for growth and reproduction.

Greenstein and Thompson²⁰ have pointed out that the enzyme patterns of malignant tissues are remarkably similar both qualitatively and quantitatively, irrespective of their tissue of origin. Taylor, Pollack, and Williams²¹ have shown that tumors are remarkably uniform in their B-vitamin content. From this "... it is concluded that malignant neoplasms of various types and from various animals tend to have similar cellular metabolism forming in effect a common tissue type." The similarities between malignant and embryonic tissues have been pointed out above. Normal tissues on the other hand vary markedly in their concentration of various enzymes. This appears to be directly related to the variations in function from tissue to tissue.

The thought emerges that possibly all cells, since they have a common origin from a mass of undifferentiated embryonic tissue composed of similar cells, may have a common group of enzymes which form a basic "primitive" group, and, superimposed on these, acquired in the process of differentiation, a second group which varies from tissue to tissue depending on differences in function, making the performance of the cell's highly specialized tasks possible.

Thus we may picture the normal adult cell as containing two groups of enzyme systems. The one common to all cells, embryonic, malignant, or normal adult, which is specific for the requirements of growth and reproduction. The cell depends on these for its regenerative capacities. This group requires but small concentrations of certain of the B-vitamins. The other group de-

be most active. Thus the cells at the base of the tumor adjacent to the nutrient supply of normal tissue will grow; the tumor will expand and invade the subadjacent normal tissues.

Summary

From facts recently accumulated by various scientific groups and the suggestive evidence presented by a number of clinical investigators, a possible mechanism for the production of malignancy has been postulated. According to the concept outlined, neoplastic cells arise from foci where recurrent cell division is occurring in response to the stimulus to repair and regeneration. Some external factor interferes with the completion of the enzyme pattern of the regenerating cell and prevents it from acquiring the enzyme systems required for the highly specialized functions of the fully differentiated cell. Under these circumstances, in an effort to adapt to its environment the cell is forced to revert to its primitive embryonic enzyme group which can function efficiently under the restricted conditions imposed. This primitive group is especially geared for growth and reproduction. After many cell divisions (cell generations) without the completed enzyme systems, the cell by gradual stages reverts completely and assumes the morphologic and behavior characteristics of a primitive embryonic cell. Much of the activity of such a cell is influenced by various body hormones with specific growth-stimulating properties. There is considerable evidence to suggest that a chronic subclinical vitamin deficiency is one external factor which can affect the regenerating cell in this way. It is possible that various agents, chemical carcinogens, neoplastic-producing x-rays, viruses, and other factors which have been implicated in carcinogenesis may act in essentially this fashion.

It has been recently pointed out by a number of independent authorities^{20, 21} that malignant tissues regardless of species origin or of their site of origin within the host, are biochemically so similar as to constitute a common tissue type. Williams,²³ in commenting upon this striking similarity, states: "This remarkable resemblance between cancers, regardless of what animal they arise in, what tissue they come from, or how they are induced, we believe to be a highly important and revealing fact and one which strongly suggests a common etiology."

Some phases of the concept presented in the above are based on suggestive evidence alone, more confirmatory evidence is to be desired. It is, however, presented at this time as the suggestive evidence and confirmed factual findings welded into this interpretation appear to offer a plausible mechanism for the production of various forms of malignant disease while invoking nothing more unusual than the disordered function of the known biologic properties of the individual cell.

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above, they were present in the cervical cytology picture of patients who as a rule also showed evidence of a chronic subclinical thiamine deficiency and chronic cervicitis. As one would expect, the process of evolutionary reversion is a gradual one and occurs only after many cell generations (cell divisions). These findings also imply that the atypical morphologic forms seen may be regarded themselves as evidence of chronic hypovitaminosis.

Factors Which Determine Invasion

In general it may be stated that invasion results from a complete breakdown in the mechanism for control of growth potencies within the cell. This may result from either a continuously strong growth stimulus overcoming the cell's natural barriers or from a complete breakdown within the cell with dissolution of the barriers inherent in the cells internal structural organization.

It has been suggested that endocrine growth factors act upon the cell membrane, making it more readily permeable to the selective materials required for the enzyme systems concerned in growth activity. In the absence of the endocrine factor, therefore, the cell membrane would perform an important function in growth control. In rapidly growing anaplastic carcinoma the malignant tissue often takes on the character of a syncytium, nuclei in a mass of cytoplasm. It may be that the loss of cell membrane in such a tissue is one factor in determining its rapid growth characteristics; one of the control barriers has been entirely broken down.

There is evidence to suggest that the enzymes concerned with the specialized functions of the differentiated cell are located in the cytoplasm. It has long been recognized that the function of the nucleus is of prime importance in the processes concerned with growth and reproduction. If the specialized enzymes may be regarded as a "prepotent" group of enzymes which rapidly utilize energy materials which enter the cell for functional purposes none will be available for the nuclear enzyme systems. Thus the growth and reproduction activities of the nucleus will be held in check. A cytoplasm with highly specialized enzyme systems may then be regarded as an additional growth controlling mechanism.

We might then plausibly picture the malignant potencies of a cell as inherent in the normal functions of its nucleus and the highly developed properties for growth and reproduction which reside there. For the exercise of these functions certain materials are required. If they are supplied in ample quantities, growth proceeds at a rapid rate. However, in the normal adult specialized cell the nucleus is starved. These materials are kept from it by two barriers—the surrounding cytoplasm which contains a "prepotent" set of enzyme systems, and the cell membrane. Once the cytoplasmic barrier has been altered by chronic subnutrition, growth activity in the cell is under the influence of cell membrane permeability alone. The total growth potencies of the cell may then be readily provoked by a strong growth promoting endocrine factor.

Once these two growth controlling agencies are broken down, the cells of the neoplastic focus which are supplied with the most nutrient material will

CERVICAL CANCER IN YOUNG GIRLS

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CARCINOMA of the uterine cervix in young girls differs from the disease in adult women in three important respects: its apparently worse prognosis, the preponderance of adenocarcinoma over the epidermoid type, and its extreme rarity. The literature records only four five-year survivals among patients under 21 years of age with cervical cancer (Pollack and Taylor, 1947). In this same age group approximately two-thirds of all carcinomas of the cervix are of the glandular type, in contrast to the relatively low incidence of 5 per cent or less with which this type of cervical cancer appears among older women. So rare is carcinoma of the cervix in minors that such cases constitute gynecologic curiosities.

In a statistical tabulation of 937 deaths from uterine cancer in 1870, Glatter recorded only two patients under the age of 21 years. Gusserow (1886) could not add a single authentic case when he reviewed 3,385 cases of carcinoma of the cervix sixteen years later. The number of acceptable cases still stood at two in 1905 (Steffen). Several cases have been reported in more recent years, however. In the latest review of the literature on carcinoma of the cervix during the first two decades of life, Pollack and Taylor (1947) collected thirty cases and added one of their own, a girl of 18 years, bringing the total to thirty-one cases. The acceptable total may be somewhat less than this, however, for the following reasons. In one instance the same patient has obviously been the subject of two separate reports (MacDonald, 1929; Morse, 1930). In another case (Amesse, 1932) the cervical origin of the tumor is not clear; and in still others, originally thought to be carcinomas, the diagnosis was changed later to endothelioma (Philipp, 1907), teratoma (Adams, 1916), and adenocarcinoma of the fundus (Lockhart, 1935), respectively. On the other hand, occasional cases, such as those of Little (1896), Schreiner and Wehr (1934), and Kelly (1939), apparently have been overlooked. Regardless of the exact number of authentic cases, cervical cancer in girls of 20 years or younger is extraordinarily rare. It is my purpose, therefore, to report two additional cases of carcinoma of the cervix in young girls, one aged 12 years, the other aged 19 years.

CASE 1.—D. C. (R. H. No. 9595), a 12-year-old white schoolgirl, was admitted to the Roosevelt Hospital on April 13, 1920, because of persistent leucorrhea of several months' duration. She had had an appendectomy six weeks previously in another city. A large polypoid, hemorrhagic, friable tumor was discovered involving the anterior lip of the cervix and extending to the anterior vaginal wall. A piece of the tumor was removed for biopsy, the pathologic report being adenocarcinoma of the cervix. The tumor cells were arranged in two ways, some in the form of small irregular acini, but the larger number forming long anastomosing strands, which were supported by thin cores of connective tissue stroma. The cells were large and cylindrical, with faintly staining cytoplasm and oval reticular nuclei (Fig. 1). On April 15, 1920, one hun-

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Comment

Case 1 is the seventh reported instance of carcinoma of the cervix in girls age 12 or under. Table I shows the salient features of each. The tumor described by MacDonald and by Morse is included as a cervical carcinoma because it was so stated to be, although their reports do not exclude the possibility of its fundal origin. Adenocarcinoma was the histologic type of each of the six tumors for which this feature was recorded.

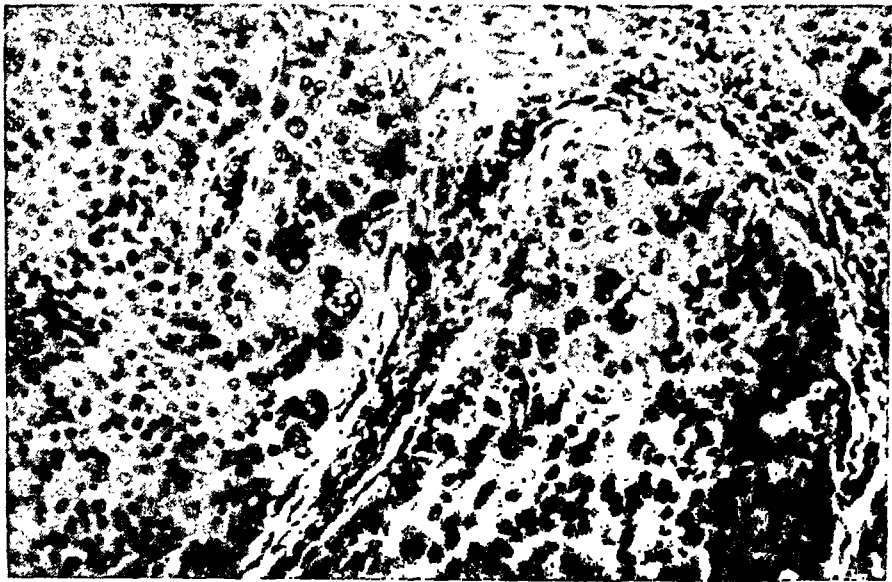


Fig. 2.—Case 2. Epidermoid carcinoma of cervix in a girl aged 19 years.

TABLE I. REPORTED CASES OF CARCINOMA OF CERVIX IN GIRLS AGED 12 YEARS OR UNDER

| AUTHOR | YEAR | AGE | TYPE | TREATMENT | SURVIVAL |
|----------------------------|------|-----------|----------------|---------------------------------|---------------------------------|
| Ganghofer | 1888 | 8 years | Adenocarcinoma | Excision and cau- terization | Died in 2 weeks with variola |
| Glöckner | 1908 | 7 years | Adenocarcinoma | Laparotomy | No follow-up |
| Bumm | 1909 | 7 months | Not stated | Laparotomy | No follow-up |
| Findley | 1924 | 6 months | Adenocarcinoma | Hysterectomy | No follow-up |
| MacDonald | 1929 | 10 years | Adenocarcinoma | Exploratory; | Died within a year |
| Morse | 1930 | | | x-ray | |
| Scheffey and Craw- ford | 1932 | 22 months | Adenocarcinoma | X-ray | Died in 6 weeks |
| Speert | 1947 | 12 years | Adenocarcinoma | Radium | Died in 15 months |

The striking difference in the relative incidence of histologic types of cervical cancer between children and adults has not been explained. The low incidence of cervical carcinoma in general in young girls is not surprising. The phenomenon which requires explanation is the disproportionately lower incidence of epidermoid cancer in children. The juvenile years constitute a period of relative quiescence in the squamous epithelium which lines the vagina and covers the portio of the cervix. A membrane which is normally 20 to 30 cell layers thick in mature women may be only one-fourth or one-fifth this thickness in prepubertal girls. Mitoses are correspondingly less frequent in children. This difference explains the increased susceptibility of the juvenile vaginal membrane to infection and its diminished capacity for repair. Meyer's studies

dred milligrams of radium were applied in the cervix for twelve hours. A similar application was made for eight hours on April 24, and the patient was discharged from the hospital on April 27. She was readmitted on June 9 of the same year for another treatment. During the interim she had been symptomatically well and was completely relieved of the vaginal discharge. The cervix appeared much improved, but there was still a slightly rough and nodular area on the right side, extending to the right anterior vaginal wall. On June 11 one hundred milligrams of radium were inserted into the vagina against the cervix for six hours. Another application of 50 mg. of radium for eight hours was made on August 11, bringing the total radium dosage to 3,000 milligram hours. At this time the cervix seemed to be essentially normal except for paracervical induration, which was interpreted as a cicatricial reaction to the previously administered radium. On Oct. 25, 1920, the patient was reported to be suffering with abdominal pain, vomiting, weight loss, and lumps in the groin. She went progressively downhill and died at home on July 7, 1921, fifteen months after treatment was begun.

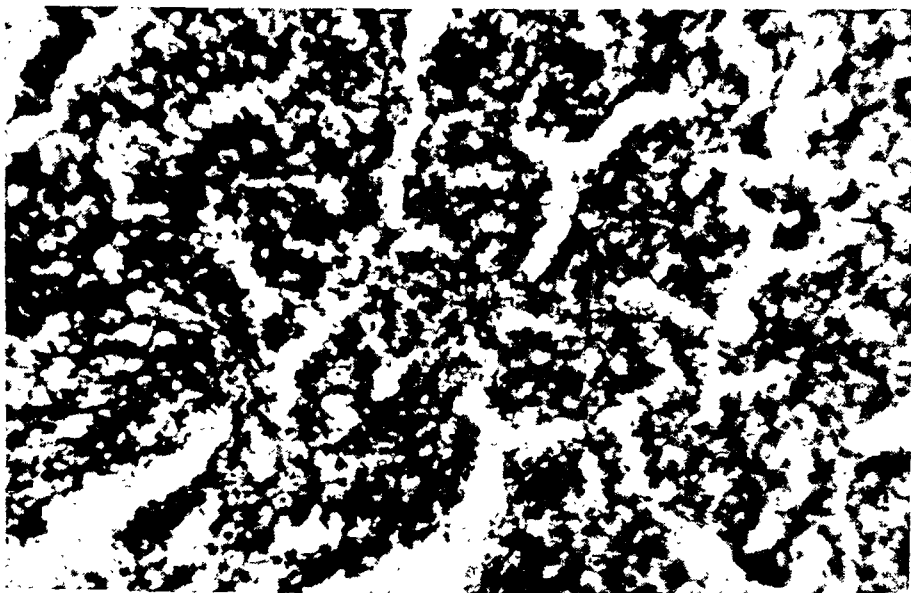


Fig. 1.—Case 1. Adenocarcinoma of cervix in girl aged 12 years.

CASE 2.—M. G. (R. H. No. 8225), a 19-year-old single, nulliparous, white Polish office worker, was admitted to the Roosevelt Hospital on Oct. 27, 1918, complaining of vaginal discharge which she had had since her menarche at the age of 9 years; and backache, weakness, and nervousness of three months' duration. Her menses had been profuse and prolonged, the flow coming at intervals of fourteen to twenty-eight days, and lasting for ten days. Her last menstrual period began Oct. 6, 1918. Examination under anesthesia revealed an intact hymen and a soft polypoid mass at the external cervical os. Neither the fundus of the uterus nor the adnexa could be felt. Dilatation and curettage and trachelorrhaphy were performed on October 28. Sections of the cervical tissue showed epidermoid carcinoma of the cervix (Fig. 2); the curettings were diagnosed as "chronic hypertrophic endometritis" (endometrial hyperplasia). On November 27, radical abdominal hysterectomy, bilateral salpingo-oophorectomy, and appendectomy were carried out. No residual tumor was found in routine sections of the extirpated uterus and cervix. The patient was last seen on Oct. 22, 1919, eleven months after operation, at which time she seemed completely well, had gained 43 pounds, and showed no evidence of tumor recurrence.

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on the embryology of the vaginal mucosa and lower cervix (Novak, 1944) have shown these parts of the reproductive canal to be of a single origin, namely from the urogenital sinus. The thickness of its surface epithelium is clearly related to estrogenic control. In a similar fashion, hormonal function is believed to be one of the major factors which control the advance or regression of the junction between the stratified squamous epithelium and the columnar epithelium within the cervical canal. In young girls in whom estrogenic activity is at a low and presumably constant level, the line of junction between the two varieties of epithelium within the cervix would be expected to remain relatively static. In mature women, on the other hand, higher estrogenic titers and the fluctuations which result from the menstrual cycles and from pregnancies tend to make the cervical squamocolumnar epithelial junction a region of unrest in which the squamous epithelium now advances, now retreats.

It is precisely at this junction between the zones of squamous and columnar epithelium that most epidermoid cervical cancers originate. The conditions of unrest which might conceivably favor neoplastic development in the squamous epithelium are lacking in prepubertal girls. In Case 2, on the contrary, where the cervical tumor was of the epidermoid type, an associated lesion of the endometrium was found, which is generally regarded as an indication of excessive or unopposed estrogenic stimulation, namely endometrial hyperplasia. Recent studies of vaginal cytology (Ayre, 1947) suggest exactly this type of hormonal aberration as a common concomitant of epidermoid cervical cancer in adults.

The poor prognosis which has been associated with cervical carcinoma in children may be the result of inadequate treatment rather than any specific peculiarity of the disease. This suggestion will be put to test by subsequent cases in which the patient is treated by currently approved techniques of radium and x-ray. Most of the reported cases have occurred before the modern era of radiotherapy. Case 1 represents the only patient in the group under 13 years of age who received the benefit of radium. In the collected series of Pollack and Taylor, only six patients had been treated with radium, the only two authentic five-year cures being among this group.

Summary

1. Two cases of cervical carcinoma are reported in girls aged 12 and 19 years, respectively.
2. This report includes the seventh recorded case of cervical cancer in girls aged 12 years or under. The salient features of these cases are tabulated.
3. In contrast to the preponderance of epidermoid cervical cancer in adult women, adenocarcinoma is the commonest type of cervical carcinoma in young girls. A theoretical explanation for this difference is suggested.
4. The poor prognosis associated with cervical cancer in young girls in the past may be the result of inadequate treatment.

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Table II shows the birth weights of the infants in this series and the incidence of each weight group in patients with adequate or normal pelvis. The average birth weight for the infants in this series was 7 pounds, which is slightly below the average birth weight for infants born in this hospital.

TABLE II. INFANT BIRTH WEIGHT

| | 3 POUNDS OR LESS | 3 TO 5½ POUNDS | 5½ TO 6 POUNDS | 6 TO 7 POUNDS | 7 TO 8 POUNDS | 8 TO 9 POUNDS | 9 TO 10 POUNDS | OVER 10 POUNDS |
|---------------|---------------------|-------------------|-------------------|------------------|------------------|------------------|-------------------|-------------------|
| Total | 5 | 4 | 2 | 12 | 23 | 9 | 3 | 3 |
| Normal pelvis | 4 | 3 | 1 | 10 | 14 | 8 | 3 | 1 |

One-half of the patients with abnormal pelvis gave birth to infants weighing 7 to 8 pounds. Almost 25 per cent of the infants were well above average birth weight, i.e., 8 pounds or more. Only three of these 15 infants weighing 8 pounds or more were born to women with abnormal pelvis: one, weighing 8 pounds 10½ ounces, was delivered by internal podalic version and breech extraction of a para vii with a history of previous difficult deliveries and measurements indicating a slightly contracted pelvis; the second, weighing 10 pounds 15¾ ounces, was delivered by internal podalic version and breech extraction with aftercoming head forceps of a para iii with slightly contracted pelvis; and the third, weighing 10 pounds 1 ounce, was delivered by Kerr cesarean section of a para vii with just minor pelvis and a history of previous long and hard labors. Some degree of relative disproportion was probably present not only in these three latter cases, but in all of the cases with large infants. Therefore, instead of only 18 cases of disproportion (i.e., taking pelvic measurements alone as the criterion), there were 30 cases in all with some degree of cephalopelvic disproportion; or almost one-half of the cases showed either small pelvis by measurement or an average pelvis with an oversized infant.

There were no pelvic tumors mentioned in any of the 61 cases. Special search was made through the hospital records of these patients, but none had pelvic tumors recorded either on previous or subsequent hospital admissions.

The cord was around the neck in only one case. Diagnosis of face presentation was made early in labor in this case and confirmed by x-ray. The patient, a 36-year-old para iii, was delivered by classical cesarean section and the cord was found wrapped around the infant's neck three times. There was no incidence of abnormal enlargement of the neck in this series.

The incidence of monstrosities in this series was high. Of the 61 infants, seven, or over 11 per cent, were monstrosities. Five of these infants were anencephalic monsters, while the other two were acraniorachischisis. This figure is somewhat lower than the average given in most texts for the incidence of monstrosities in face presentation.

Actual measurements of the fetal heads were not made in this series. However, no comments were made in any of the cases concerning unusually long heads noticed on routine neonatal examination.

Placenta previa occurred in only one case in this series. Cesarean section was performed in this case and a face presentation was an incidental finding rather than an indication for the cesarean section.

Morbidity and Mortality.—There were no maternal deaths in this series, and the maternal morbidity (using the standard of morbidity as a temperature of 100.4° F. occurring during any two 24-hour periods through the tenth day excluding the first twenty-four hours) was 8.7 per cent. There were five cases of endometritis, one case of pyelitis, and one case of incisional abscess. The history of the latter case illustrates the results of poor obstetric judgment:

M. W., 30-year-old primiparous patient, was admitted to Lying-In Hospital from another institution after having had ruptured membranes for one week and after twenty-one

FACE PRESENTATION*

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(From the Philadelphia Lying-In Hospital)

OBSTETRIC textbooks give the incidence of face presentation as one in every 200 to 300 deliveries. Posner and Buch¹ reported in 1943 the incidence at Harlem Hospital, New York, as one face presentation among every 529 deliveries. From Jan. 1, 1931, through July 31, 1946, at the Philadelphia Lying-In Hospital there have been 61 face presentations in a total of 35,163 deliveries, or an incidence of one face presentation among every 576 deliveries. The purpose of this paper is an analysis of these 61 cases as to etiology, management, and end results.

Etiology

The causes for face presentation are usually listed as maternal and fetal, and are divided as follows:

A. Maternal causes

1. Faulty axis of the uterus
 - a. Lateral version
 - b. Forward position (pendulous abdomen of the high multiparous patient)
2. Contracted pelvis, or normal pelvis with large baby
3. Pelvic tumors

B. Fetal Causes

1. Protrusion of the anterior part of the neck
 - a. Several coils of cord around the neck
 - b. Enlarged thyroid gland, etc.
2. Anencephaly and other forms of monstrosities
3. Dolicocephaly elongation of the occipital arm of the head lever)
4. Placenta previa

Lateral version of the uterus was not mentioned in any of these cases. Table I shows the parity of the cases and the type of pelvis. There were almost an equal number of primiparous patients and multiparous patients; but almost 60 per cent of the multiparous patients, or 30 per cent of the total patients, had

TABLE I

| PARITY | TOTAL | TYPE OF PELVIS | | |
|------------------|-------|----------------|------------|------|
| | | GYNECOID | JUSTOMINOR | FLAT |
| Para i | 29 | 18 | 9 | 2 |
| Para ii | 13 | 13 | 0 | 0 |
| Para iii | 9 | 7 | 2 | 0 |
| Para iv | 3 | 1 | 2 | 0 |
| Para v and above | 7 | 4 | 2 | 1 |
| Total | 61 | 43 | 15 | 3 |

had two or more children. Of the 29 primiparous patients, there were 11, or 38 per cent, with some form of pelvic abnormality, while of the 32 multiparous patients there were only seven, or 22 per cent, showing pelvic abnormality.

*Presented by invitation at a meeting of the Philadelphia Obstetrical Society.

TABLE V

| | ANTERIOR | TRANSVERSE | POSTERIOR | TOTAL |
|---------|----------|------------|-----------|-------|
| Left | 12 | 5 | 13 | 30 |
| Right | 14 | 5 | 4 | 23 |
| Unknown | 3 | 0 | 1 | 4 |

No explanation can be offered for this deviation from the accepted average except the small size of the series. However, it is noticed that Posner and Buch's series also deviated from the expected incidence.

There were two cases of compound presentation involving the hand in this series. No mention was made that the prolapse of the hand was considered to be an etiologic factor in either of these cases.

TABLE VI. MANAGEMENT

| TYPE OF DELIVERY | PRIMIPARAS | | | | MULTIPARAS | | | | TOTAL |
|---|---------------|-----------------|----------------|--------------|---------------|-----------------|----------------|--------------|-------|
| | ANTE- RIOR | TRANS- VERSE | POSTE- RIOR | UN- KNOWN | ANTE- RIOR | TRANS- VERSE | POSTE- RIOR | UN- KNOWN | |
| Spontaneous | 3 | 0 | 2 | 2 | 8 | 3 | 1 | 0 | 19 |
| Low forceps | 6 | 2 | 3 | 0 | 4 | 0 | 0 | 0 | 15 |
| Midforceps | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| Low forceps with rota- tion | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 |
| Midforceps with rota- tion | 0 | 2 | 0 | 0 | 0 | 1 | 0 | 0 | 3 |
| Internal podalic ver- sion and breech ex- traction | 1 | 0 | 1 | 0 | 0 | 1 | 2 | 0 | 5 |
| Internal podalic ver- sion and breech ex- traction with for- ceps on aftercom- ing head | 2 | 0 | 0 | 0 | 2 | 1 | 3 | 1 | 9 |
| Kerr cesarean | 0 | 0 | 2 | 0 | 2 | 0 | 0 | 0 | 4 |
| Classical cesarean | 0 | 0 | 0 | 1 | 0 | 0 | 2 | 0 | 3 |
| Porro cesarean | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 |

Type of Delivery.—Table VI gives the method of delivery for this series according to the position of the infant, and separates primiparous patients from multiparous patients. It is interesting to note that 19, or almost one-third, of the patients delivered spontaneously, including two primiparous patients and three multiparous patients with posterior positions, all of which rotated spontaneously. Another 25 per cent of the patients were delivered by forceps without forceps rotation. So there was a total of six posterior and four transverse positions which rotated spontaneously (one transverse was rotated manually and then delivered by low forceps). Internal podalic version and breech extraction was used in almost 25 per cent of the cases; cesarean section was the method of delivery in, eight, or 13 per cent of the cases. Table VII lists the indications for cesarean sections in this series. Two of the sections were done electively before the onset of labor, one with placenta previa as the indication and the other after x-ray diagnosis of face presentation was made. The one Porro cesarean section has been reviewed earlier. The remaining five were done from five to eight hours after the onset of labor. Table VIII gives the fetal mortality

TABLE VII. INDICATIONS FOR CESAREAN SECTION

| | |
|--|---|
| Cephalopelvic disproportion | 5 |
| Malpresentation (face) | 2 |
| Placenta previa (face presentation incidental) | 1 |
| Total | 8 |

hours of hard labor. Forceps delivery had been attempted in the other institution resulting in a third degree laceration of the perineal floor. Pelvic measurements taken on admission showed a just minor pelvis, and examination revealed posterior face presentation. The patient was delivered by Porro cesarean section of a stillborn boy weighing 7 pounds 8 ounces. There was a rather stormy postoperative course and an incisional abscess formed. When the abscess was opened and drained the temperature returned to normal. The perineal floor was repaired on the thirteenth postoperative day.

The fetal mortality for face presentation was nearly four times the average fetal mortality for the hospital, but compares favorably with most statistics for face presentation. A total of twelve, or 19.7 per cent, of the babies were either stillborn or died before the tenth day. There were eight, or over 13 per cent, stillbirths and four, or 6.5 per cent, neonatal deaths. This is an uncorrected fetal mortality; of these twelve infant deaths, seven were monstrosities and one was a normal infant weighing less than two pounds. Table III gives the fetal mortality correlated with birth weight. There was 100 per cent mortality among the five infants weighing 3 pounds or less (however, four of these were monstrosities, and the only normal infant weighed 1 pound, 13 ounces). It might be expected that the larger babies would sustain more injuries in delivery, but of the 38 infants weighing over 7 pounds, there was only one stillborn (the case delivered by Porro cesarean section cited previously) and two neonatal deaths, one of which was a monster.

TABLE III. INFANT MORTALITY

| | 3 POUNDS OR LESS | 3 TO 5½ POUNDS | 5½ TO 6 POUNDS | 6 TO 7 POUNDS | 7 TO 8 POUNDS | 8 TO 9 POUNDS | 9 TO 10 POUNDS | OVER 10 POUNDS |
|------------------------|---------------------|-------------------|-------------------|------------------|------------------|------------------|-------------------|-------------------|
| Total No. in- fants | 5 | 4 | 2 | 12 | 23 | 9 | 3 | 3 |
| Total | | | | | | | | |
| Mortality | 5 | 1 | 1 | 2 | 1 | 2 | 0 | 0 |
| Stillborn | 3 | 1 | 1 | 1 | 1 | 0 | 0 | 0 |
| Neonatal | 2 | 0 | 0 | 1 | 0 | 2 | 0 | 0 |
| Monsters | 4 | 1 | 0 | 1 | 0 | 1 | 0 | 0 |

There was mention in most of the cases of the presence of edema and bruising of the face. In addition to these two not uncommon complications there were four infants with evidence of trauma. Table IV correlates the type of delivery with the form of injury. All of these infants improved and were discharged from the hospital in apparently good condition.

TABLE IV

| |
|--|
| <i>Internal Podalic Version and Breech Extraction</i> |
| 1. Dislocated shoulder |
| 2. Cyanosis, listlessness, and xanthochromia of the spinal fluid |
| <i>Midforceps Rotation and Delivery</i> |
| 1. Traumatic cellulitis of the head |
| <i>Low Forceps Delivery</i> |
| 1. Cyanosis of the face |

Position.—According to most textbooks the incidence of the various positions in face presentation correlates closely with the incidence of the occipital presentation to which it corresponds, i.e., 85 per cent of face presentations are said to be right mentoposterior and left mentoanterior corresponding to left occipitoanterior and right occipitoposterior occipital presentations. However, in this series there was an almost equal distribution among left mentoanterior, right mentoanterior, and left mentoposterior, and right mentoposterior occurred only four times. The position was mentioned on the chart in 57 of the 61 cases. Table V gives the incidence of each position in this series.

was a neonatal death following internal podalic version and difficult breech extraction in a para vii with a slightly contracted pelvis and history of long labors and difficult deliveries. Well-timed cesarean sections in these two cases, avoiding the traumatic deliveries (or attempted delivery), would undoubtedly have resulted in living healthy infants; and in the first case earlier section would have prevented the necessity for Porro cesarean. The two other infant deaths were due to nonpreventable causes. One case came into the hospital with a dead baby, the cause of antepartum death of the infant could not be determined; the other death was due to compression of an occult prolapse of the cord resulting in intra-partum death of the infant a few hours before delivery.

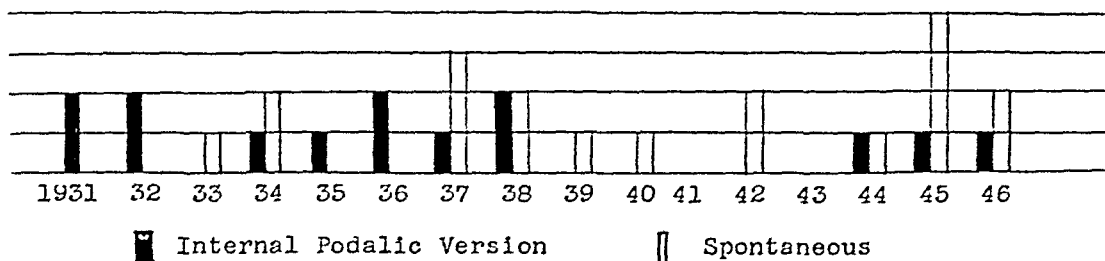


Fig. 1.—Yearly incidence of version.

There has been a definite trend in this hospital toward more conservatism in the treatment of face presentation. The fact that over 50 per cent of the cases delivered spontaneously or with only low forceps proves out the dictum, "If a 'face' is progressing, leave it alone." Fourteen, or almost 25 per cent, of the cases were managed by internal podalic version and breech extraction. This means that over one-half of the cases requiring major operative procedure for delivery were managed by version. Fig. 1 shows the incidence of internal podalic version occurring in each year covered by this paper, and also shows the incidence of spontaneous delivery for the same period. Eleven of the versions were done between 1931 and 1938, inclusive, while only three have been done since 1938. On the other hand, between 1931 and 1938 only eight patients, or 25 per cent, delivered spontaneously, while since 1938 there were eleven, or almost 40 per cent, delivered spontaneously. This parallels the trend of this clinic to do fewer versions.

An incidence of 13 per cent cesarean sections seems high, yet when we consider that only one infant was lost among these eight sections and it was lost because the section was not done early enough, cesarean section for face presentation with any degree of disproportion seems justified. Indeed, if cesarean section had been done in at least one other case (the version and difficult extraction) probably another infant would have been saved. With the maternal mortality and morbidity of cesarean sections decreasing, the value of this procedure as a means of obtaining a living infant is increasing.

Summary

1. A series of 61 face presentations occurring in 35,163 consecutive deliveries in Philadelphia Lying-In Hospital is analyzed.
2. The classification and etiology of this condition are discussed.
3. There were no maternal deaths.

correlated with the type of delivery. It is surprising to note that the more traumatic types of deliveries as forceps rotation and aftercoming head forceps were not associated with any deaths.

TABLE VIII. INFANT MORTALITY VS. TYPE OF DELIVERY

| | SPONTANEOUS | LOW FORCEPS | INTERNAL PODALIC VERSION AND BREECH EXTRACTION | CESAREAN |
|------------------------------------|-------------|-------------|--|----------|
| Stillborn | | | | |
| Premature | 0 | 0 | 0 | 0 |
| Term | 2 | 0 | 0 | 1 |
| Monsters | 1 | 2 | 1 | 0 |
| Neonatal deaths | | | | |
| Premature | 1 | 0 | 0 | 0 |
| Term | 0 | 0 | 1 | 0 |
| Monsters | 2 | 1 | 0 | 0 |
| Total (normal) infant mortality | 3 | 0 | 1 | 1 |

The average duration of labor for both primiparous and multiparous patients was far below the accepted normals. For the primiparous patients labor varied from one hour, twenty-three minutes (for a 2 pounds 12 ounce infant) to thirty-two hours, thirty-four minutes (for a 2½ pounds anencephalic monster), and the average duration of labor was fourteen hours. In the multiparous patients the length of labor varied from two hours (for a 9 pound infant) to thirty-two hours, fifty-eight minutes (for a 7 pounds 3 ounce infant), and the average duration of labor was eleven hours and thirty-six minutes.

Discussion

Considering each of the commonly accepted etiologic factors for face presentation (and excluding multiparity per se as a factor) only 37 of the cases in this series present a definite cause for the malpresentation:

| | |
|------------------------------------|----------------|
| Abnormal pelvis | 18 (1 monster) |
| Normal pelvis with large infant | 12 (1 monster) |
| Monstrosities (not included above) | 5 |
| Placenta previa | 1 |
| Cord around the neck | 1 |
| | <hr/> 37 |

Therefore, almost 40 per cent of the cases occurred in women with clinically normal pelves, having normal average or smaller than average infants, and with no complications of etiological value. Whether these patients did have normal pelves can certainly be questioned, and the occurrence of a face presentation in a supposedly normal pelvis would call for a careful check of all measurements at subsequent pregnancies.

According to this small series the prognosis for both the mother and the infant does not seem grave. Although the maternal mortality for the hospital is generally low, the absence of a maternal mortality in this series cannot be disregarded. At first glance an infant mortality of 19.8 per cent seems high; but a corrected figure (excluding monsters and infants under 3 pounds birth weight) of four, or 6.5 per cent, compares favorably with the general average for the hospital for the years included in this series. Two of these four deaths were a result of poor obstetric judgment. The one case was brought in from another institution with a dead baby after attempted forceps delivery; the other

RELATION OF MOTHERS' DIETS TO STATUS OF THEIR INFANTS AT BIRTH AND IN INFANCY

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THE effect of the mother's prenatal diet upon the status of her child at birth and its growth progress during the first year is still a controversial subject. McLester¹ states "... lack of protein in the mother's diet, unless extreme, will not affect the development of the fetus, for in case of need, the tissues of the mother are broken down to secure the amino acids necessary for construction of fetal tissues; it is only when starvation is extreme that the fetus suffers." Yet Burke, Harding, and Stuart² concluded from a study of 216 women and their offspring that "a significant relationship was found to exist between the protein content of the mother's diet during pregnancy and the birth length of her infant. This increase in length can be demonstrated with each additional increment of protein in the prenatal diet. . . . When the birth weights of the infants were considered in relation to the average number of grams of protein in the mothers' diet during pregnancy, it was found that an increase in birth weight could also be demonstrated with each additional increment of protein in the prenatal diet."

The efforts of various other workers suggests that material dietary deficiencies are capable of altering the structure and function of the developing fetus. Ebbs and Tisdall³ have recorded a high correlation between the adequacy of the vitamin content of the mother's diet, the nature of delivery, and state of the infant at birth, and the infant's progress. Burke, Stuart, and associates⁴ have reported an even higher relationship between the mother's diet and these factors, as well as the heights and weights of the newborn infants. Dieckmann's work⁵ has further emphasized the importance of prenatal diet. Warkany⁶ at Cincinnati has been able to produce certain skeletal defects in newborn rats by maintaining the rat mothers on grossly inadequate diets. There is as yet some question as to what elements of inadequacy are primarily responsible for these defects. Sontag and Munson,⁷ working with rats, were able to show that drastic alterations in vitamin D and calcium intake were expressed in the chemical constitution of the offspring. Seegars⁸ was able to show that the offspring of rats grossly deficient in protein intake during pregnancy produced newborn rats of distinctly smaller size and weight.

Despite the fact that there is evidence that certain deficiencies in the maternal diet will produce alterations in the structure and function of the developing fetus, it is not yet clear at what level of dietary deficiency such effects become apparent. Neither humans nor laboratory animals respond in increased growth rate in a direct arithmetical ratio to the amounts of food they ingest. They possess to some degree, rather, what might be called a nutritional homeostasis. That is, within limits, they utilize more efficiently or less well the food they ingest according to their growth and maintenance needs. A person of

4. There were 12 fetal deaths, however, only four of these deaths occurred in babies normally formed and weighing more than three pounds. Two were due to poor obstetric judgment; one to prolapsed cord; and one to antepartum death, cause unknown.

5. There was a high incidence of monstrosities; five were of the anencephalic type, the other two acraniorachischisis.

6. There was almost equal distribution between left mentoanterior, right mentoanterior, and left mentoposterior position; no explanation for the deviation from the expected incidence is offered.

7. The prognosis for mother and infant is generally good.

8. The majority of patients can be safely delivered spontaneously or by low forceps. Cesarean section proved to be the safest method of delivery in those cases in which disproportion was present. Internal podalic version is not being used as often as in earlier years.

Reference

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Discussion

DR. ROY W. MOHLER.—I think a report of this kind is very important because it constitutes the clinical findings where a large volume of obstetric work is done, and shows pretty clearly how seldom this complication arises in obstetrics. A few pertinent comments are in order.

It is instructive to know that 30 per cent of these patients delivered spontaneously, 25 per cent were delivered by forceps, 25 per cent by internal podalic version and extraction, and the remainder by cesarean section. In only five instances was the face presentation with recognized disproportion the indication for cesarean section. The results from the management of these cases were satisfactory when one reviews the tables critically.

Dr. Rudolph's presentation seems to indicate that face presentation of a fetus is a formidable complication in obstetric work; that no individual will encounter the complication frequently enough to acquire a familiarity which will enable him to manage the condition along any set plan. An effort should be made to recognize the condition fairly early. This can be accomplished by developing the habit of making more frequent and careful vaginal examinations in labor. These statistics have shown that one has ample time to observe what is happening with these patients in labor and that in the absence of frank disproportion, most of them will develop into chin anterior positions. After rotation has occurred, some will deliver spontaneously, others will need to be delivered with forceps. The presentations which remain chin posterior are the real problems, and it is in these few instances that some radical procedure must often be used. It is in these instances where good, sound obstetric experience and judgment must be exercised. For one, individual internal podalic version may be the procedure of choice; for another, individual cesarean section may be the procedure of choice. Whichever is the best and safest procedure for the individual to use, that is the procedure for him to choose.

DR. PHILIP F. WILLIAMS.—I would like to ask if attempts were made into any of these cases to convert a face into a vertex presentation to facilitate delivery?

DR. GEORGE PORRECCA.—I would like to know how often the diagnosis of face presentation was made prior to the patient going into labor?

DR. RUDOLPH (Closing).—There was one instance in which manual version was attempted when the cervix was approximately three fingers' dilated, but it was unsuccessful.

In one case the diagnosis of face presentation was made prior to delivery and cesarean section was resorted to.

months of gestation and the subsequent careful study of their offspring. One factor studied has been the diets of these women. The quantity of data we have now accumulated seems to us to justify analysis in an attempt to determine whether from it relationships between prenatal nutrition, the status of the infant at birth, and its subsequent growth progress can be demonstrated. This paper will present one portion of such an analysis, namely, a comparison between the mothers' average daily protein intake and the birth weights, birth lengths, and growth progress of their infants. Rate of appearance of ossification centers in relation to mothers' protein intake will also be considered.

Material

The 205 mothers and their infants considered in this study have been under observation at the Institute for an extended period of time. These subjects volunteered their cooperation not because it was solicited, but because they were genuinely interested in participating in the study. As a group, they might be described as belonging to the upper middle class. They are white women of well-blended American stock and are residents of Ohio. They cover a considerable income range, particularly since some of the observations were made during the 1931 to 1934 period. The majority of them have not been so pressed financially as to be unable to afford nutritious food, but many had poor dietary habits. Most of these mothers were under observation during the last six or seven calendar months of pregnancy and were seen at least once a month. During the last part of this period they were examined once a week or oftener. Laboratory data such as basal metabolism rates, hemoglobin, red cell counts, and hematocrit readings were collected at regular intervals during pregnancy. A later study will present such data and its relationship to nutritional intake.

Dietary records were obtained in the following manner. Each pregnant woman was asked to record daily the exact foods she had consumed and as nearly as possible the exact amounts. She was urged not to rely on her memory as to what she had eaten the day previously. In general, dependence upon memory even for one day in the recording of diets must be considered fallacious. There are few persons who can give an accurate account of all the foods eaten, together with a description of their quantities twenty-four hours later. Each mother was made to feel that if she occasionally missed a day's record because of unusual circumstances such as company or a holiday away from home, no one would be concerned about it. Most of these records were kept for a period of sixteen weeks or longer, a considerable number of them for six or seven months. Each week's record consisted of seven consecutive days so as to eliminate a preponderance of unusual days as Sundays or washdays. Once a month the nutritional histories were brought in and checked with the patient by a nutritionist in order to be sure that no misunderstanding existed and that the records were reliably kept and were representative.

At no time was any mother instructed as to what she should eat. Not one of these mothers could therefore have any sense of guilt because she had not adhered to a diet we had suggested as being necessary for the adequate protection of her growing infant. This point is extremely important in acquiring dietary records, because few patients care to brave the displeasure of a diet-conscious physician for a small item as a bottle of milk. Most of them feel it is much easier to report what is expected.

From this battery of nutrition records quantitative analyses were made in terms of average daily intake of protein, calories, minerals, and the various vitamins. A full description of our method of data collection and analysis is

low caloric intake will utilize very effectively every gram of carbohydrate he gets. On the other hand, in an individual who is fed so much sugar that the threshold of his kidneys is exceeded, some of the surplus will be discarded in the urine. Calcium and phosphorus are treated in a somewhat similar way. Added to this tempering influence is also the homeostatic action of the body in maintaining blood levels of numerous elements within relatively narrow ranges by utilizing body stores of protein, glycogen, calcium, phosphorus, etc., as well as food. Digesting four pounds of beefsteak a day for a couple of weeks by an adequately nourished individual will not raise substantially the level of blood proteins, and even amino acids in the blood are only temporarily increased, and to a limited extent. On the other hand, if no protein at all is ingested for a few days there is relatively little drop in blood proteins, and amino acids do not disappear from the blood stream. They are supplied rather from the protein tissues of the body which act as protein stores.

Such factors then act as buffers between the precipitous fluctuations of a mother's dietary intake and the continuous need of the fetus for body building and energy nutriment. Until we begin to test the abilities of such homeostatic mechanisms to maintain maternal blood levels of essential elements, it is not impossible that we may find it difficult to demonstrate conclusively relationships between maternal dietary intake to the size and condition of the infant at birth. It is entirely possible for extremes of maternal dietary deficiency in protein to express themselves in terms of small or inadequate offspring. Yet it does not necessarily follow that the mother whose daily protein intake is 75 Gm. will produce an infant inferior in size or quality to the woman whose intake is 85 Gm. per day. It may be true even that if the dietary intake is 65 Gm., no deficiency of the infant can be demonstrated; or perhaps 55 Gm. might be the limit. It is also probable that there are individual differences in this respect—differences perhaps dependent upon the various metabolic functions of the mother as well as the adequacy of maternal stores of various food elements at the beginning of pregnancy. It may very well make an appreciable difference to the fetus whether his mother is a six foot woman weighing two hundred pounds attempting to support herself and him on a daily intake of 65 Gm. of protein, or whether she weighs a hundred pounds and ingests the same amount of protein. If so, it would be difficult to assume that an infant will necessarily be defective or in poor condition at birth if the mother's protein diet is 53 Gm. per day instead of 60. Perhaps all these factors, plus individual differences in absorption from the alimentary tract, would prevent our finding a very high correlation between *ingestion* and the size of the newborn infant, providing we are dealing with a group whose nutritional level is not gravely deficient. No such marked effect upon size of infant at birth could be expected in our group as that shown by Smith⁹ and by Antonov.¹⁰ Both of these investigators studied the effects of partial starvation of populations at certain periods of the war, and were able to show conclusively that maternal diet affected size of the newborn.

For the past ten years a part of the study of the Fels Research Institute has included the close observation of pregnant women during the last six or seven